Sex differences in medial prefrontal and parietal cortex structure in children with disruptive behavior

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ABSTRACT

Sex differences in brain structure in children with disruptive behavior disorders (DBD) remain poorly understood. This study examined sex differences in gray matter volume in children with DBD in a priori regions-of-interest implicated in the pathophysiology of disruptive behavior. We then conducted a whole-brain analysis of cortical thickness to examine sex differences in regions not included in our hypothesis. Exploratory analyses investigated unique associations between structure, and dimensional measures of severity of disruptive behavior and callous-unemotional traits. This cross-sectional study included 88 children with DBD (30 females) aged 8–16 years and 50 healthy controls (20 females). Structural MRI data were analyzed using surface-based morphometry to test for interactions between sex and group. Multiple-regression analyses tested for sex-specific associations between structure, callous-unemotional traits, and disruptive behavior severity. Boys with DBD showed reduced gray matter volume in the left ventromedial prefrontal cortex (vmPFC) and reduced cortical thickness in the supramarginal gyrus, but not girls compared to respective controls. Dimensional analyses revealed associations between sex, callous-unemotional traits, and disruptive behavior for amygdala and vmPFC volume, and ventrolateral prefrontal cortex cortical thickness. Sex-specific differences in prefrontal structures involved in emotion regulation may support identification of neural biomarkers of disruptive behavior to inform target-based treatments.

1. Introduction

Disruptive behavior disorders (DBD), including Oppositional Defiant Disorder and Conduct Disorder, are characterized by the presence of clinically significant levels of irritability/anger, aggression, noncompliance, or antisocial behavior (American Psychiatric Association, 2013). DBD affect a large number of children worldwide (Polanczyk et al., 2015) and are a common reason for referral to mental health services (Kessler et al., 2005; Costello et al., 2014). Further, in children with DBD, the presence of callous-unemotional (CU) traits, defined by a lack of guilt, empathy, or remorse, can be associated with life-course persistent antisocial and aggressive behaviors (Rowe et al., 2010) as well as a greater risk for developing other co-occurring psychiatric conditions (Odgers et al., 2008; Abram et al., 2015; Moffitt, 2017). Despite a growing number of functional and structural neuroimaging

studies investigating the neural underpinnings of DBD (Alegria et al., 2016; Rogers and De Brito, 2016), few studies have examined sex differences in brain structure in children with DBD or the possible interaction of sex with CU traits. Here, we investigate sex differences in gray matter volume and cortical thickness in regions implicated in the pathophysiology of disruptive behavior in a well-characterized sample of children with DBD.

Developmental models of aggression suggest perturbations in neural circuitry that support successful emotion processing and regulation. Specifically, abnormalities of the amygdala and ventral prefrontal cortex (PFC) contribute to impaired emotion regulation and reactive aggression, including over-reactivity of the amygdala (Herpertz et al., 2008; Passamonti et al., 2010; Viding et al., 2012) and underactivity in prefrontal regulatory regions, particularly the ventromedial and ventrolateral prefrontal cortex (vmPFC and vlPFC, respectively) in children

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with DBD (Coccaro et al., 2007; Beauchaine et al., 2008; Decety et al., 2009; Aghajani et al., 2017; Ibrahim et al., 2019). Thus, a leading hypothesis is that disruption in amygdala-vmPFC circuitry sets the stage for onset of disruptive behavior, particularly given the shared reciprocal connections between the vmPFC and amygdala (Price and Drevets, 2010; Milad and Quirk, 2012; Motzkin et al., 2015) and essential role of this circuitry in adaptive affect or emotion regulation (Buhle et al., 2014; Etkin et al., 2015; Silvers et al., 2016). Collectively, these results suggest that the onset of DBD could be reflected in the integrity of the amygdala-vmPFC circuitry. In addition to the amygdala-vmPFC circuitry, it should be noted that reduced activation in parietal regions has also been suggested in youths with DBD (White et al., 2012; Alegria et al., 2016; Klapwijk et al., 2016). Recent meta-analyses reported reduced gray matter volume in youth with disruptive behavior in regions implicated in emotion generation/reactivity and regulation (Raschle et al., 2015; Noordermeer et al., 2016; Rogers and De Brito, 2016). Of relevance to the current study, reduced gray matter volume was reported in the amygdala (Sterzer et al., 2007; Huebner et al., 2008; Noordermeer et al., 2016; Aghajani et al., 2017) as well as the ventral prefrontal cortex including the vmPFC in children with DBD relative to healthy controls (Huebner et al., 2008; Dalwani et al., 2015; Sebastian et al., 2016). However, one study reported increased gray matter volume of the vmPFC in a community sample of boys with conduct problems (De Brito et al., 2009). Another study did not find significant gray matter volume differences between DBD and control groups using a whole-brain, volumetric analysis (Michalska et al., 2015).

In comparison to studies of gray matter volume, relatively fewer structural MRI studies have examined cortical thickness in children with DBD. Although complementary to gray matter volume that is measured in cubic millimeters, cortical thickness is defined as the amount of gray matter located between the gray-white interface and the pia mater, and is measured in millimeters (Gennatas et al., 2017). Moreover, there is evidence to suggest that youth with DBD show reduced cortical thickness in the vmPFC (Fahim et al., 2011; Jiang et al., 2016; Smaragdi et al., 2017). However, prior studies of gray matter volume and cortical thickness in DBD consisted of predominately males and were not powered to test sex differences in brain structure despite the known sex-differences in developmental trajectories in cortical structures (Gennatas et al., 2017).

The neuroanatomical mechanisms of sex differences in disruptive behavior remain unclear, despite known differences in the prevalence of disruptive behavior in boys versus girls (Moffitt and Caspi, 2001; Keenan et al., 2010; Demmer et al., 2017). One study of adolescents and young adults reported opposite patterns of gray matter volume disruptions in the anterior insula in males and females with conduct disorder compared to gender-matched controls (Fairchild et al., 2013). Another study of sex differences in cortical thickness in adolescents with conduct disorder reported that males showed lower and females showed higher cortical thickness in the supramarginal gyrus relative to gender-matched control groups (Smaragdi et al., 2017). Thus, to advance understanding of sex differences in brain structure in youths with DBD that could inform identification of sex-specific brain-based biomarkers, several areas remain to be addressed.

First, there is a need to explore the utility of surface-based morphometry measures in children with DBD who have a broader range of disruptive behavior symptom severity. The few existing surface-based morphometry studies of disruptive behavior were conducted in samples of adolescents and young adults with more severe forms of conduct disorders (Hyatt et al., 2012; Wallace et al., 2014; Fairchild et al., 2015; Smaragdi et al., 2017). Smaragdi et al. (2017) reported reduced cortical thickness in the left vmPFC and a sex-by-group interaction in the right supramarginal gyrus in a sample of youths with conduct disorders aged 14–18 years. Another study (Wallace et al., 2014) reported reduced cortical thickness in the bilateral superior temporal/inferior parietal cortex in youths aged 10–18 years with conduct disorder. Hyatt et al. (2012) showed reduced cortical thickness

in the left superior temporal/parietal/supramarginal gyrus as well as in the left inferior temporal gyrus in a sample of 19 youths with conduct disorder in comparison to 24 healthy controls aged 12–18 years. Lastly, Fairchild et al. (2015) showed reduced cortical thickness in the right superior temporal gyrus in 36 males with conduct disorder compared to 20 healthy control males aged 16–21 years. Additionally, there was a negative association between supramarginal gyrus/inferior parietal cortex thickness and severity of conduct disorder symptoms (Fairchild et al., 2015). Second, surface-based morphometry offers several advantages to understand structural abnormalities in children. For instance, surface-based morphometry measures of cortical volume and thickness are more robust relative to voxel-based morphometry (Klein et al., 2009, 2010; Clarkson et al., 2011; Rajagopalan and Pioro, 2015) because it can distinguish between different cortical properties with distinct etiologies and developmental trajectories (Panizzon et al., 2009). Third, surface-based morphometry may be advantageous for identifying additional regions that have not been incorporated in developmental models of disruptive behavior. For example, surface-based morphometry studies of children with conduct problems have consistently reported reduced cortical thickness in the temporal cortex including the superior (Fairchild et al., 2015) and inferior temporal gyri (Hyatt et al., 2012) as well as the supramarignal gyrus/inferior parietal regions (Hyatt et al., 2012; Wallace et al., 2014; Fairchild et al., 2015; Smaragdi et al., 2017). Here, we address these prior limitations by including a well-characterized sample of children with disruptive behavior disorders (n = 88) in the age range from 8–16 years and 50 gender- and age-matched controls to examine sex differences in disruptive behavior-related structural abnormalities using surface-based morphometry.

Because CU traits can have suppresser effects on the association between measures of disruptive behavior and brain structure and function, we used a dimensional approach to simultaneously model CU traits and severity of disruptive behavior, while controlling for the variance of the other, to account for potential suppressor effects between these variables (i.e., variance of one dimension not shared with the other). While abnormalities in gray matter volume of the amygdala (Aghajani et al., 2017; Cardinale et al., 2018) and ventral prefrontal cortex (Fairchild et al., 2013) are associated with CU traits in children with DBD, suppressor effects may conceal the relationship between the dependent variable, such as functional or structural networks, and the predictor variable, such as CU traits or disruptive behavior in youths (Sebastian et al., 2012, 2016; Cardinale et al., 2018; Ibrahim et al., 2019). Here, we test how sex-specific differences in brain structure of children with DBD can be related to the dimensional measures of CU traits and severity of disruptive behavior.

Lastly, disruptive behavior tends to appear during preschool years and Oppositional Defiant Disorder has the onset between 6 and 8 years of age (Ezpeleta et al., 2019). However, to our knowledge, all studies of brain morphology of DBD were conducted with adolescents (with the exception of the study by Wallace et al. (2014) that included an age range from 10 to 18 years). Our study addresses this limitation by investigating sex differences in cortical thickness and gray matter volume in 8- to 16-year-old children with disruptive behavior disorders. We selected measures of cortical thickness and gray matter volume because we reasoned that this would enable comparison to prior structural imaging studies of youth with conduct problems that have used surface-based morphometry and similar structural measures.

The primary aim was to investigate sex-by-group interactions in gray matter volume in a priori regions including the amygdala and vmPFC in children with DBD relative to gender-matched healthy controls. These regions were selected based on recent meta-analyses of structural MRI studies of disruptive behavior (Noordermeer et al., 2016; Rogers and De Brito, 2016). The second aim was to examine sex-by-group interactions in cortical thickness in children with DBD relative to gender-matched healthy controls. We conducted a whole-brain analysis of cortical thickness in order to assess regions not included in our hypotheses and to

allow comparison to prior structural MRI work in youth with conduct problems using similar methodology. Given the paucity of surface-based morphometry studies examining sex differences in brain structure in youth with DBD, it was not possible to make strong *a priori* predictions for sex-by-group interactions, particularly the direction of sex effects on brain structure. Nevertheless, we expected that boys and girls with DBD would show sex-specific differences in gray matter volume and cortical thickness. Post hoc tests were also conducted to assess the robustness of findings in an IQ-matched sample and differential patterns of brain structure in subgroups based on levels of CU traits.

We also conducted exploratory and follow-up analyses to test sex-by-group interactions using dimensional measures of severity of disruptive behavior. For these exploratory analyses, we examined the unique associations between brain structure and CU traits using the Inventory of Callous-Unemotional Traits (ICU) (Frick, 2003) and severity of disruptive behavior using the Child Behavior Checklist (CBCL) Externalizing Behavior Problems scale (Achenbach and Rescorla, 2001). We hypothesized that gray matter volume and cortical thickness would differentially predict disruptive behaviors in girls and boys after controlling CU traits. For follow up analyses, we systematically assessed the impact of covariates related to co-occurring symptoms of ADHD and internalizing behaviors in region-of-interest (ROI) and whole-brain analyses. Given the influence of age on brain structure development (Gennatas et al., 2017), we also tested age-related differences between DBD and healthy

control children (group-by-age interactions) and potential interactions with sex (sex-by-group-by-age interactions). Recent longitudinal structural studies suggest attenuation of cortical maturation (i.e., reduced cortical thinning) and exaggeration of subcortical maturation in the emergence of disruptive behavior in youth (Oostermeijer et al., 2016; Bos et al., 2018; Muetzel et al., 2018). Thus, even though exploratory in nature, we expected adolescents with DBD to show increased volume and thickness in prefrontal regions compared to younger children with DBD relative to controls, and the opposite pattern for amygdala volume.

2. Methods

2.1. Participants

The sample included 88 children with Disruptive Behavior Disorders (DBD group; 30 females) and 50 typically developing healthy controls (HC group; 20 females) matched for age and IQ. All participants were aged 8–16 years. Table 1 shows demographic and clinical characteristics of participants. Details regarding inclusion and exclusion criteria for the study are provided in the Supplement. Children with DBD participated in a treatment study of behavior therapy for anger and aggression (Sukhodolsky et al., 2016) and this paper reports structural MRI and clinical characterization data that were collected prior to initiating the treatment. Children with disruptive behavior were recruited from the

Table 1
Participant Demographics and Clinical Characteristics.

Variable	Total Sample			Subgroups based on sex and disruptive behavior disorder				
	HC n = 50	DBD n = 88	p value	Female DBD n = 30	Female HC n = 20	Male DBD n = 58	Male HC n = 30	p value
Age, years (SD)	12.3 (1.8)	11.7 (2.2)	.08	11.3 (2.5)	12.5 (1.7)	11.9 (1.9)	12.2 (1.9	.17
Mean IQ[a] (SD)	111.2 (13.2)	106.8 (13.3)	.07	105.4 (15.5)	108.9 (16.2)	107.6 (12.8)	112.8 (10.8)	.19
Race (n, %)			.65					.93
White	33 (66)	64 (72.7)		21 (70)	14 (70)	43 (74.1)	19 (63.3)	
Black	9 (18)	13 (14.8)		6 (26.1)	4 (20)	7 (12.1)	5 (16.7)	
Asian/Pacific Islander	1 (2)	1 (1.1)		0	0	1 (1.7)	1 (3.3)	
American Indian/Alaska Native	0	2 (2.3)		1 (3.3)	0	1 (1.7)	0	
Other/More than one race	7 (14)	8 (9.1)		2 (6.7)	2 (10)	6 (10)	5 (16.7)	
Ethnicity (n, %)			.35					.34
Hispanic	6 (12)	17 (19.3)		7 (23.3)	4 (20)	10 (17.2)	2 (6.7)	
Non-Hispanic	44 (88)	71 (81)		23 (76.7)	16 (80)	48 (82.8)	28 (93.3)	
Mean CBCL aggression T score (SD)	50.7 (2.2)	75 (6.8)	<.001[b,c]	74.4 (6.8)	50.8 (2.2)	75.3 (6.9)	50.7 (2.2)	<.001[b,d]
Mean CBCL externalizing T score (SD)	41.1 (7.2)	71.3 (4.3)	<.001[b,c]	71.4 (3.8)	41.3 (7.7)	71.2 (4.7)	40.9 (6.8)	<.001[b,d]
Mean CBCL internalizing T score (SD)	42.1 (6.7)	62.7 (10.4)	<.001[b,c]	59.8 (11.4)	40.8 (6.8)	64.2 (9.7)	42.8 (6.6)	<.001[b,d]
Mean ICU total score (SD)	14.8 (6.0)	33.4 (9.7)	<.001[b,c]	32.1 (8.9)	13.5 (5.1)	34.3 (10.2)	15.8 (6.5)	<.001[b,d]
DSM-5 diagnosis (n, %)								
Oppositional defiant disorder		62 (70.5)		19 (63.3)		43 (74.1)		.33
Conduct disorder		11 (12.5)		3 (10)		8 (13.8)		.74
Disruptive behavior disorder NOS		2 (2.3)		1 (3.3)		1 (1.7)		1
DMDD[e]		15 (17)		6 (20)		9 (15.5)		.77
Attention-deficit/ hyperactivity disorder		64 (73)		17 (56.7)		47 (81)		.02[b]
Anxiety disorder		21 (23.9)		7 (23.3)		14 (24.1)		1
Depressive disorder		5 (5.7)		0		5 (8.6)		.16
Medication (n, %)		36 (40)		6 (20)		30 (51.7)		.006[b]
Type of medication (n, %)								
Stimulants		28 (31.8)		3 (10)		25 (43.1)		.002[b]
Alpha-2 agonists		16 (18.2)		1 (3.3)		15 (25.9)		.01[b]
Antidepressant		7 (8)		0		7 (12.1)		.09
Neuroleptics		9 (10)		2 (6.7)		7 (12.1)		.71
Mood stabilizers		1 (1.1)		0		1 (1.7)		1
Benzodiazepines		0		0		0		

Note: Diagnoses of disruptive behavior disorder and comorbid disorders were made using the *Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version* (K-SADS-PL).
Abbreviations: CBCL, Child Behavior Checklist; DBD, disruptive behavior disorder; DMDD, Disruptive mood dysregulation disorder; HC, healthy controls; ICU, Inventory of Callous-Unemotional Traits.
[a] Full-scale IQ measured by the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1997) or the Differential Ability Scales-II (Elliott, 2007).
[b] Significant group differences at p < 0.05, Bonferroni corrected for pairwise comparisons, except for Chi-square test for categorical variables and independent samples T-test.
[c] DBD > HC.
[d] DBD Female > HC Female; DBD Female > HC Male; DBD Male > HC Male; DBD Male > HC Female.
[e] According to DSM-5, oppositional defiant disorder diagnosis is not assigned to children who also met criteria for DMDD.

outpatient child psychiatry clinic at the Yale University Child Study Center and from outreach to the local schools, pediatricians and mental health providers. One of the inclusion criteria for the treatment study was a T-score of 65 or greater on the Aggressive Behavior Scale of the Child Behavior Checklist (CBCL) (Achenbach and Rescorla, 2001). Children were allowed to have co-occurring psychiatric disorders such as ADHD and anxiety if the presence of co-occurring disorders did not require immediate treatment. Untreated PTSD and severe depression were exclusionary criteria based on the rationale that these disorders present with pressing treatment needs. In addition to high levels of aggression on the dimensional measure (i.e. CBCL), all children met criteria for Oppositional Defiant Disorder (ODD), Conduct Disorder, or Disruptive Mood Dysregulation Disorder (DMDD). All subjects who were assigned DMDD diagnoses also met criteria for ODD and following DSM-5 only one diagnosis (i.e., DMDD) was assigned (American Psychiatric Association, 2013). Of note, the current study was developed in response to the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) initiative, which calls for explicating the core dimensions of psychopathology to evaluate the neural underpinnings of symptom dimensions across diagnostic boundaries (Insel and Wang, 2010). Thus, children were included if they met a cut-off score for clinically significant aggressive behavior and these included a subgroup of children who met DSM-5 criteria for DMDD. Children were also required to be able to complete structural and functional MRI scans. Thus, this paper reports on children with disruptive behavior disorders and high levels of aggression (indexed by CBCL aggression scale T score > 65) who were seeking treatment for disruptive behavior. Healthy control children recruited would be matched on age, gender and IQ to children with the clinical sample. Fifty healthy control participants were recruited from the community via advertisements. Thus, 90 structural scans of participants in the DBD group and 50 structural scans of participants in the healthy control group were available for this analysis. Six structural scans from the DBD group were excluded due to high motion during scanning and two more scans were excluded after quality control assessment of reconstruction and segmentations due to artifact and segmentation errors. Thus, a total of 138 participants with high quality structural MRI data were included in the final analysis. Each participant's parent provided informed consent according to specifications by the institutional review board at the Yale University School of Medicine. Each child provided verbal and written assent.

2.2. Clinical assessment

Children received a comprehensive diagnostic evaluation that included the *Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version* (K-SADS-PL) (Kaufman et al., 2016), a structured interview with excellent reliability that was conducted with the parent and child by an expert clinician to establish DSM-5 diagnoses of Disruptive Behavior Disorders as well as co-occurring psychopathology. Parents also completed the CBCL (Achenbach and Rescorla, 2001). Full scale IQ was evaluated with the *Wechsler Abbreviated Scale of Intelligence (WASI)* (Wechsler, 1997) or the *Differential Ability Scales-II* (Elliott, 2007). Parents completed demographics and medical history forms.

Children were included in the disruptive behavior group if they met DSM criteria for a DBD (oppositional defiant disorder and/or conduct disorder) based on the diagnostic evaluation with the K-SADS. In addition, children with disruptive behavior were also required to meet a cut-off criterion of a T score $\geq$ 65 on the *Aggressive Behavior* scale of the parent-rated CBCL, a well-established measure of child psychopathology (Achenbach and Rescorla, 2001). This score is 1.5 standard deviations above the mean in the standardization sample and represents a cut-off for a clinically significant level of aggression. The *Aggressive Behavior* scale includes 16-items reflecting inappropriate anger outbursts as well as verbal and physical aggression. HC participants were required to have no current or past history of psychiatric or neurological disorders and a

CBCL-aggression T-score below 55.

Parents completed the Inventory of Callous-Unemotional Traits (ICU) (Frick, 2003), a 24-item questionnaire with excellent internal consistency and construct validity (Kimonis et al., 2008). The ICU total score was used as a dimensional measure of CU traits. The parent-rated CBCL Externalizing Behavior Problems Scale score (Achenbach and Rescorla, 2001) was used as a dimensional measure of severity of disruptive behaviors. Internal reliability was high for the ICU ($\alpha = 0.90$), CBCL Aggressive Behavior Problem scale ($\alpha = 0.94$), and CBCL Externalizing Behavior Problem scale ($\alpha = 0.93$).

2.3. MRI acquisition & processing

Structural MRI data was collected using a Siemens MAGNETOM Tim Trio 3 T scanner. High-resolution structural MRI data was collected using a Siemens MAGNETOM Tim Trio 3 T scanner with an upgrade for echoplanar images (EPI). A T1-weighted high-resolution anatomical scan was obtained for each participant for co-registration purposes: repetition time (TR) = 2530 ms; echo time (TE) = 3.31 ms; 1 mm isotropic voxels; 176 slices; flip angle = 7°; matrix size = 2562; field of view (FOV) = 256 mm.

Standard preprocessing and analysis was conducted using FreeSurfer v6.0 (http://surfer.nmr.mgh.harvard.edu) surface-based cortical reconstruction, which has been previously described (Fischl and Dale, 2000; Winkler et al., 2012). This involved cortical surface reconstruction, cortical thickness estimation, cortical parcellation, and subcortical segmentation. The surface-based morphometry approach employs information related to intensity and continuity from the entire 3D MRI volume in segmentation and deformation procedures (Dale et al., 1999). Thus, rather than reliance upon absolute signal intensity, this approach also uses spatial intensity gradients across tissue classes (Fischl and Dale, 2000). The reconstruction estimated the white surface, comprising the white-gray matter interface, and the pial surface comprising the gray matter-cerebrospinal fluid interface as described and validated in previous publications (Dale et al., 1999; Fischl et al., 1999; Schaer et al., 2008). Subcortical gray matter structures were identified and generated using the FreeSurfer automated volumetric segmentation procedure (Fischl et al., 2002). Estimated total intracranial volume for each subject also was obtained and used to control for inter-individual variability in global brain size. Trained researchers (K.I., G.H., G.M.), who were blind to group assignment, visually inspected the quality from all neuroimaging outputs and surface reconstructions to ensure accuracy of segmentations, artifact, motion, and image quality (see *Structural MRI Quality Control* in the **Supplement** for full details of the quality control assessment). There were 146 participants with structural MRI scans. Six participants were excluded due to motion (youths with DBD). Following inspection of cortical reconstruction and segmentations, two additional participants were excluded (youths with DBD) due to improper cortical reconstruction, segmentations and artifact. Thus, 138 participants with high quality structural imaging data were included in the final analysis. Total gray matter volume was higher in males overall compared to females (all Ps <.001) as expected (Giedd et al., 1999; Gennatas et al., 2017). Importantly, post-hoc tests showed that there were no significant differences in total gray matter volume between males with DBD and male controls ($p = 0.6$) or between females with DBD and female controls ($p = 1.0$) (see Supplement and Table S8 for full details). Post-hoc tests also showed that there were no significant differences in IQ between males and females ($t_{136} = 0.996$, $p = 0.32$) and a contrast analysis showed no differences in IQ between DBD males and females, and respective controls ($F_{3,137} = 0.41$, $p = 0.19$) (see Table 1).

2.4. Region-of-interest analysis of gray matter volume

Our primary aim was to test sex differences in gray matter volume in *a priori* regions-of-interest involved in emotion regulation (amygdala, vmPFC) that were selected based on structural meta-analyses in youth

with conduct problems (Noordermeer et al., 2016; Rogers and De Brito, 2016). Thus, we conducted a focused region-of-interest analysis of gray matter volume using the FreeSurfer automated parcellation procedures derived from the Desikan-Killiany Atlas (Fischl et al., 2004; Desikan et al., 2006). During this stage, neuroanatomical labels are automatically assigned to each voxel based on probabilistic information of spatial relationships. We extracted estimates of gray matter volume for both hemispheres because it might be advantageous to understand any lateralization effects. For subcortical gray matter volume, we focused on the bilateral amygdala given that perturbations in this is region are consistently implicated in DBD. For cortical gray matter volume, we focused on the vmPFC/medial orbitofrontal cortex because aberrant structure and function of this region is associated with DBD as well as emotion regulation impairments (Buhle et al., 2014; Silvers et al., 2016). Multivariate GLM model was conducted in SPSS v26 for a priori estimates of cortical and subcortical gray matter volume to examine the interaction between sex and group. The GLM model included covariates for total intracranial volume to control for inter-individual variability in global brain size as well as IQ, age, and race/ethnicity. All models used a statistical threshold of significance set at $p < 0.05$. To control for multiple comparisons, a false discovery rate (FDR) correction was applied to all a priori regions ($\alpha = .05$) that combined both cortical and subcortical bilateral regions for the vmPFC and amygdala. FDR correction was conducted using the Benjamini-Hochberg algorithm in R (p.adjust function).

Additional follow-up analyses were conducted that controlled for both ADHD and internalizing symptoms. The Swanson, Nolan, and Pelham-IV Questionnaire (SNAP-IV) (Swanson et al., 2001; Bussing et al., 2008) total score was used as a continuous measure of ADHD symptoms, which is a widely used scale and well-validated measure of ADHD symptoms. The CBCL Internalizing Behavior Problem scale score was used as a continuous measure of internalizing behavior. Additional details on these measures are provided in the supplement (see *Supplemental Analyses for ADHD and Internalizing Behaviors*). We also investigated age-related differences between the groups (group-by-age interaction) and interactions with sex (sex-by-group-by-age interactions).

2.5. Whole-brain analysis of cortical thickness

Our second aim was to examine sex-by-group interactions in cortical thickness for regions not included in our hypotheses. Thus, we conducted a whole-brain analysis that was modeled based on a recent study of sex differences in cortical thickness in adolescents with conduct disorder (Smaragdi et al., 2017). The whole-brain analysis was conducted in FreeSurfer using a full-factorial general linear model (GLM) for each hemisphere, Bonferroni-corrected for laterality, and smoothed using a 10mm-full-width/half-maximum Gaussian kernel. The GLM model tested for effects of sex-by-group interactions. All models included total intracranial volume as a covariate to control for differences in individual brain size, IQ, age, and race/ethnicity. First, a vertex-wise/cluster-forming threshold of $p < 0.001$ (two-tailed) was used. Next, results were corrected for multiple comparisons at a whole-brain level using a Monte Carlo z-field simulation (Hagler et al., 2006). Clusters were then reported if they met a whole-brain corrected, cluster-wise threshold of $p < 0.05$. Additional follow-up analyses were conducted that controlled for both ADHD and internalizing symptoms. We also investigated age-related differences between the groups and with sex (group-by-age and sex-by-group-by-age interactions).

2.6. Effects of CU traits and severity of disruptive behaviors on brain structure

Next, we conducted exploratory regression analyses to assess the unique contributions of CU traits and disruptive behaviors, while accounting for the variance of the other, to sex differences in gray matter

volume and cortical thickness in the DBD group (n = 88) and in the total sample (N = 138). For gray matter volume, this was conducted in a priori regions (bilateral amygdala and vmPFC). For cortical thickness, this was conducted as a whole brain analysis to be consistent with our above workflow as well as to inform future work and identify regions associated with CU traits and externalizing behavior not initially included in our a priori hypotheses or ROI selection. This analysis was based on recent work suggesting the utility of a dimensional approach to simultaneously model CU traits and severity of disruptive behaviors to control for possible suppressor effects between these variables and to identify the unique contributions for each of these variables (Markon et al., 2011; Sebastian et al., 2012; Lozier et al., 2014; Ibrahim et al., 2019). Severity of disruptive behaviors (using the CBCL Externalizing Behavior score) and CU traits (using the ICU total score) were modeled as continuous variables with gray matter volume or cortical thickness as the dependent variable. The multivariate regression models included total intracranial volume, sex as a dichotomously coded variable (0=boys and 1=girls), CBCL Externalizing Behavior score, ICU total score, and either the interaction of sex-by-CBCL Externalizing Behavior or sex-by-ICU to examine the moderation effect of sex. All models also controlled for age, IQ, and race/ethnicity. For regression analyses of gray matter volume conducted in SPSS, alpha was set at p ≤.05. Additionally, bootstrapping 5000 times with bias-corrected 95 % CIs was implemented in SPSS. For regression analyses of cortical thickness conducted as whole brain analysis, the identical thresholds were used as described above (see *Whole-Brain Analysis of Cortical Thickness*) including a vertex-wise/cluster-forming threshold of $p < 0.001$ and a cluster-wise threshold of $p < 0.05$. For both gray matter volume and cortical thickness regression analyses, we also conducted post hoc tests to assess the contribution of ADHD and internalizing symptoms to the variance in gray matter volume or cortical thickness in regression models.

2.7. Data availability

To promote data transparency, anonymized data will be available upon reasonable request.

3. Results

3.1. Region-of-interest analysis of gray matter volume

Our hypotheses centered on sex differences in gray matter volume in youth with DBD in the amygdala and vmPFC. There was a significant interaction between sex and group for the left vmPFC ($F_{1,130} = 6.95$, FDR-corrected $p = .03$). Here, we found reduced vmPFC gray matter volume in boys, but not in girls with DBD relative to respective control groups (Fig. 1). Post hoc tests indicated that boys with DBD showed significantly reduced volume in the left vmPFC compared with control boys (t=-3.127, df = 86, p = 0.002), whereas girls with DBD did not differ from control girls (t = 0.932, df = 48, p = 0.356) (see Fig. 1). Full model results are shown in the Supplement (Table S1). The effect size η^2 for these comparisons varied from 0.03 to 0.05, which can be interpreted as small to medium effects.

Additional analyses were conducted to systematically examine the potential effect of ADHD and internalizing symptoms (see Supplement). The sex-by-group interaction for the left vmPFC remained significant after controlling for both ADHD and internalizing symptoms (p = 0.04). Finally, there were no significant interactions observed between age and group (all *P* values >0.1) or between age, group, and sex (all *P* values >0.6).

3.2. Whole-brain analysis of cortical thickness

We conducted a whole-brain analysis of sex differences in cortical thickness for regions not included in our hypothesis and for comparison
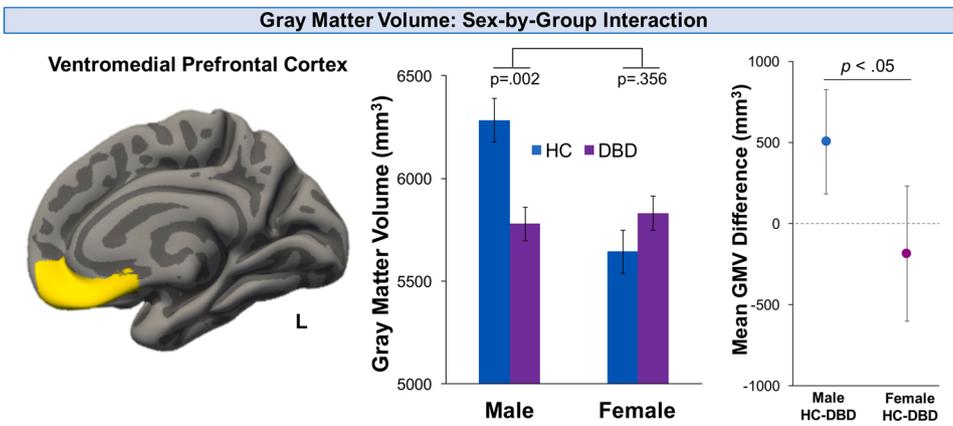
Fig. 1. Sex differences in medial prefrontal cortex gray matter volume in children with disruptive behavior disorder (DBD) relative to healthy control (HC) children. A multivariate GLM model was conducted for regions-of-interest controlling for total brain volume, IQ, age, and race/ethnicity. All results are significant at $p < 0.05$ with a false discovery-rate (FDR) correction using the Benjamini-Hochberg algorithm that was applied across all bilateral a priori regions-of-interest (ventromedial prefrontal cortex, amygdala). Regions showing a significant sex-by-group interaction included the left ventromedial prefrontal cortex (vmPFC). The vmPFC region-of-interest is displayed for visualization purposes on an inflated brain. Standard error is represented in bar graph error bars. Inset figure displays the mean difference in gray matter volume between healthy control and DBD males and between healthy control and DBD females as well as the p value for the interaction and 95 % confidence intervals.

to a recent study of cortical thickness in adolescents with conduct disorder (Smaragdi et al., 2017). A significant sex-by-group interaction was observed in the left supramarginal gyrus. Here, males with DBD showed reduced cortical thickness in the supramarginal gyrus, but not in girls with DBD relative to their respective control groups (Fig. 2; Table S2). Post hoc tests indicated that boys with DBD showed significantly reduced cortical thickness in the left supramarginal gyrus compared with control boys (t=-3.118, df = 86, p = 0.002), whereas girls with DBD did not differ from control girls (t = 0.840, df = 48, p = 0.405) (Fig. 2).

We conducted an additional whole-brain analysis to systematically examine the impact of covariates for ADHD and internalizing behaviors. Controlling for both ADHD and internalizing symptoms, we found that the main findings of sex-by-group interactions remained significant for the left supramarginal gyrus. There were also no significant two-way or three-way interactions observed between sex, group, and age for either left or right hemisphere cortical thickness.

3.3. Effects of CU traits and severity of disruptive behaviors on brain structure

We conducted exploratory analyses to test for the association between the unique variance of CU traits and severity of disruptive behaviors modeled dimensionally, and gray matter volume and cortical thickness. For gray matter volume, we conducted this exploratory analysis in the four a priori ROIs (bilateral amygdala and vmPFC).

Bootstrap analysis (with 5000 bootstrap resamples of the data with replacement) was implemented in SPSS, in which 95 % CIs not crossing zero indicate significance (α = .05). For cortical thickness, this exploratory analysis was conducted across the whole brain to be consistent with our above workflow and identify regions not included in our initial hypotheses or ROI selection.

For gray matter volume, in the total sample (N = 138), there was a significant sex-by-externalizing behavior interaction in the left vmPFC ($\beta = 0.32$, $t_{129} = 2.35$, $p = .03$, 95 % CI = [2.2, 43.5]) in which males showed a negative and females showed a positive relationship between externalizing behavior and gray matter volume after accounting for the variance in CU traits (Fig. 3). Within the DBD group, sex-by-CU traits interactions were observed for left amygdala volume ($\beta = -0.78$, $t_{79} = -2.16$, $p = .02$, 95 % CI = [-15.4, -0.5]) when accounting for externalizing behavior, in which females showed a negative and males showed a positive correlation between CU traits and amygdala volume (Fig. 3, Table S2). Controlling for ADHD and internalizing symptoms did not alter these findings for the left vmPFC ($p = 0.02$) or amygdala ($p = 0.04$).

For cortical thickness, in the total sample, there were no significant sex-by-externalizing and sex-by-CU traits interactions, or associations with CU traits. However, externalizing behavior was negatively associated with cortical thickness in a cluster in the left ventrolateral prefrontal cortex/orbitofrontal cortex; that is, children with greater severity of externalizing behavior showed reduced cortical thickness in the left ventrolateral prefrontal cortex/orbitofrontal cortex (Fig. 3). These results remained significant after accounting for ADHD and internalizing
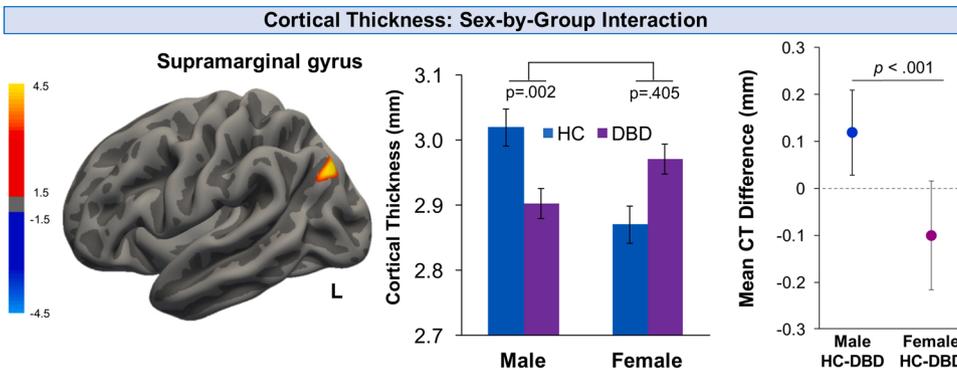
Fig. 2. Sex-by-group interactions for whole-brain analysis of cortical thickness in children with disruptive behavior disorder (DBD) relative to healthy control (HC) children. A significant sex-by-group interaction in cortical thickness was found in the left supramarginal gyrus/inferior parietal cortex. The color bar shows T values for each contrast. Standard error is represented in bar graph error bars. The model controlled for total brain volume, IQ, age, and race/ethnicity. All results are corrected for multiple comparisons at a whole-brain level using a Monte Carlo z-field simulation. Inset figure displays the mean difference in cortical thickness between healthy control and DBD males and between healthy control and DBD females as well as the p value for the interaction and 95 % confidence intervals.

Gray Matter Volume

A — Left Amygdala
In the DBD group (n=88)

B — Left vmPFC
In the total sample (N=138)

Cortical Thickness

C — Left Ventrolateral PFC/Orbitofrontal Cortex

In the total sample (N=138)
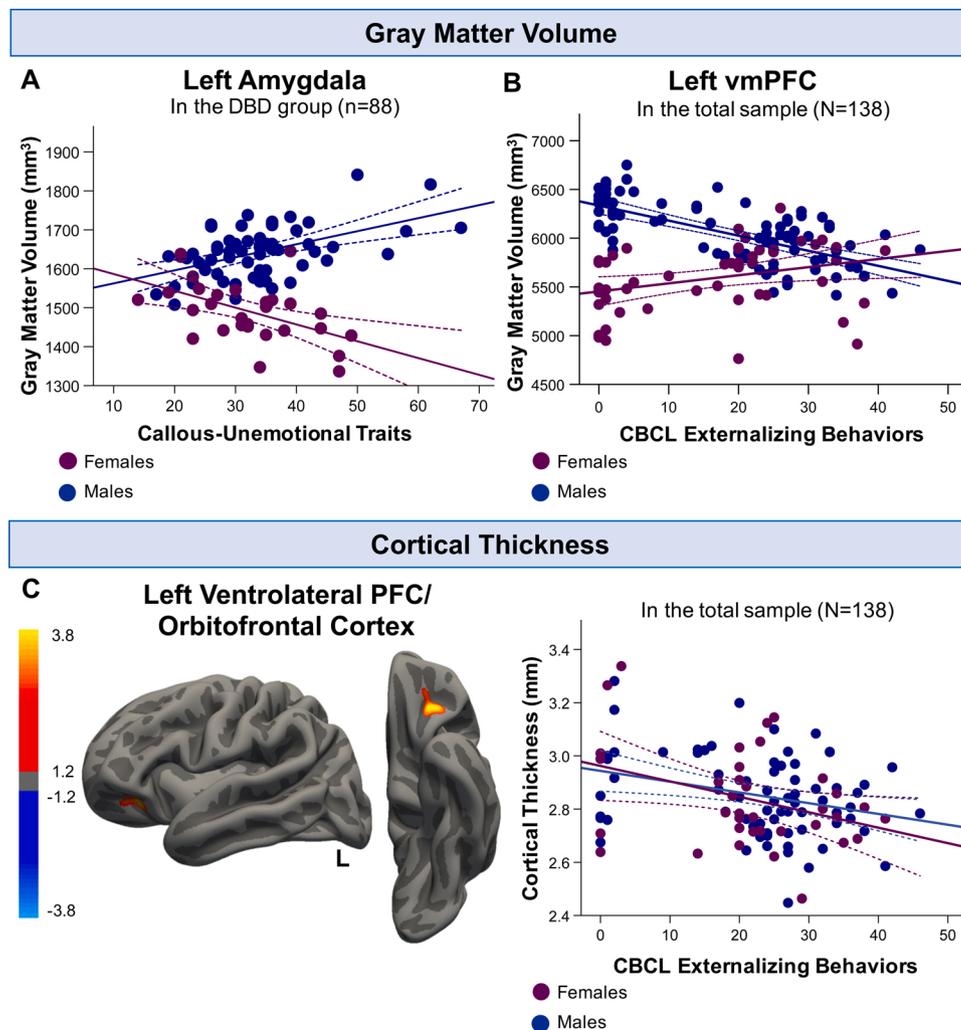
Fig. 3. Results of exploratory regression analyses showing the unique association between callous-unemotional (CU) traits, severity of disruptive behavior, and brain structure. The CBCL Externalizing Behavior score was used as a continuous measure of severity disruptive behavior and the Inventory of Callous-Unemotional Traits total score was used as a continuous measure of callous-unemotional traits. For region-of-interest analyses of amygdala and ventromedial prefrontal cortex (vmPFC) gray matter volume, bootstrapping was conducted (with 5000 bootstrap resamples of the data with replacement) in SPSS and the 95 % CIs are also reported in Tables S2. For cortical thickness, whole-brain analyses were conducted to assess regions not included in our initial hypotheses, and implemented a $p < 0.001$ cluster-forming threshold and were corrected for multiple comparisons. All regression models controlled for total brain volume, IQ, age, and race/ethnicity. In the DBD group (n = 88), there was a significant interaction between sex and CU traits for left amygdala volume ($p = .02$; adjusted $R^2 = 0.3$) after accounting for the variance in externalizing behavior (Panel A). In the total sample (N = 138), there was a significant sex-by-externalizing behavior interaction for left vmPFC volume ($p = .03$; adjusted $R^2 = 0.2$) (Panel B). For cortical thickness, in the total sample, greater severity of externalizing behavior was associated with reduced cortical thickness in the left ventrolateral prefrontal cortex/orbitofrontal cortex (Panel C). The y-axis represents gray matter volume or cortical thickness after controlling for inter-individual variability in global brain size. Purple lines show the association with CBCL Externalizing Behavior or CU traits in females, while blue lines show those observed in males. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

symptoms. In the DBD group, there was a significant sex-by-externalizing interaction for the bilateral inferior temporal gyrus. However, this cluster was no longer significant when controlling for potential confounding variables of ADHD and internalizing symptoms, and is therefore less robust and not further discussed in the main article. However, for the interested reader, we present this finding in the Supplement.

In the total sample, left amygdala volume was significantly correlated with externalizing behaviors ($r = -0.19, p = .03$). In the DBD group, there were no significant zero-order correlations between gray matter volume in regions-of-interest and CBCL Externalizing Behavior or CU traits (all $Ps > .2$). Correlations between CBCL Externalizing Behavior and ICU total did not exceed .4, suggesting low risks of multicollinearity.

3.4. Post hoc analyses

Repeating the main analyses in an IQ-matched subgroup resulted in a pattern of findings for sex-by-group interactions that was highly similar to those reported above for gray matter volume (left vmPFC) and cortical thickness (left supramarginal gyrus) (Supplement). To facilitate comparisons with prior research examining patterns of brain structure that differentiate CU subgroups, whole brain categorical analyses of cortical thickness and volume were also conducted using CU subgroups, and are presented in the Supplement. We used a cut-off score of 30 based on Docherty et al. (2017) to form CU subgroups from the parent-rated

ICU. However, we also repeated this post hoc analysis using the current sample's median ICU score (33.5) as a cut-off for comparison to the Docherty et al. (2017) cutpoint. We describe these results in the Supplement for the interested reader.

4. Discussion

This study examined sex differences in measures of gray matter volume and cortical thickness in a well-characterized sample of boys and girls with disruptive behavior. We used state-of-the-art neuroanatomical methods (surface-based morphometry) to maximize accuracy of data pre-processing. We also applied a two-pronged data analytic strategy integrating a focused study of gray matter volume in *a priori* regions implicated in DBD (amygdala, vmPFC) combined with a whole-brain analysis of cortical thickness to allow direct comparison to recent structural imaging work in youths with disruptive behavior (Hyatt et al., 2012; Wallace et al., 2014; Smaragdi et al., 2017). There are two main findings from this study. First, we found sex-by-group interactions for gray matter volume in the vmPFC; that is, reduced gray matter volume in the vmPFC was found in boys, but not in girls with DBD compared to respective controls. Second, a similar pattern of sex-by-group interactions emerged for cortical thickness in the supramarginal gyrus: that is, reduced cortical thickness in the supramarginal gyrus was found in boys, but not in girls with DBD compared to respective controls. This finding is consistent with the few surface-based morphometry studies of

cortical thickness in adolescents and young adults with DBD that report disruptions in cortical thickness in frontoparietal regions (Hyatt et al., 2012; Jiang et al., 2016; Smaragdi et al., 2017). This could also indicate the advantage of surface-based morphometry to investigate regions that have not been previously incorporated in developmental models of disruptive behaviors (i.e., parietal regions), which could be informative for developing sex-specific, brain-based biomarkers of DBD. While prior meta-analyses of voxel-based morphometry studies have reported reduced volume of the amygdala as well as the ventral prefrontal cortex in individuals with conduct problems (Noordermeer et al., 2016; Rogers and De Brito, 2016), contrary to our hypotheses, we did not find significant sex differences in gray matter volume of the amygdala in children with DBD compared to controls. However, this is also consistent with a recent study of brain structure in adolescents using surface-based morphometry, in which no significant sex differences in amygdala volume were found in youths with conduct disorder (Smaragdi et al., 2017).

The vmPFC is a region consistently implicated in the pathophysiology of DBD in functional (Coccaro et al., 2007; Beauchaine et al., 2008; Decety et al., 2009; Aghajani et al., 2017) and structural (Huebner et al., 2008; Dalwani et al., 2011; Smaragdi et al., 2017) MRI studies. The dorsal and ventral regions of the prefrontal cortex have functional and structural projections that connect to parietal and limbic regions, forming a frontoparietal and frontolimbic network that is tightly coupled with the cognitive control of emotion or emotion regulation (Milad and Quirk, 2002; Ochsner et al., 2002; Vidal-Gonzalez et al., 2006; Pessoa, 2010; Etkin et al., 2011; Arnsten and Rubia, 2012; Lückmann et al., 2014; Silvers et al., 2016). In the current study, we found a sex-by-group interaction for the left vmPFC. However, post hoc tests showed that this was driven by reduced vmPFC volume in DBD males compared to HC males, but not for DBD females compared to HC females. In contrast to a recent study that showed reduced cortical thickness of the vmPFC in children with conduct disorder (Smaragdi et al., 2017), contrary to our expectations, we did not observe a main effect of group for differences in vmPFC structure between DBD and HC youths. While structural MRI studies have shown aberrations in orbitofrontal, parietal and temporal regions in youths with DBD (Rogers and De Brito, 2016), there has been inconsistency in findings related to the ventral PFC in previous structural imaging work (Sterzer et al., 2007; Huebner et al., 2008; De Brito et al., 2009; Dalwani et al., 2011; Fahim et al., 2011; Fairchild et al., 2011; Hyatt et al., 2012). One reason for this could be variation in MRI structural methods (surface vs. voxel-based morphometry), differences in the age range across samples, and confounding effects of neural maturation that takes place at different times and rates for girls vs. boys, which is challenging to account for given that prior work has largely assessed brain mechanisms of disruptive behavior in cross-sectional studies. It is possible that the effects of sex and group may obscure clear-cut group findings, and the interactions between these variables could offer more accurate depictions of structural differences between males and females with disruptive behavior and respective controls. Additionally, our findings of sex-by-group interactions could be influenced by sex differences in the variability in brain structure (Wierenga et al., 2017). More work is needed to advance understanding of sex differences in the structural integrity of prefrontal regions involved in emotion regulation, which could inform clinical interventions that address disruptive behavior differently in boys and girls with DBD. For example, interventions could differentially target cognitive processes influenced by sex-specific structural perturbations in the ventral PFC such as decision making, social perception, and emotion regulation. Thus, future studies are needed to test whether brain structure predicts treatment response differently in girls and boys with disruptive behavior.

Whole brain analyses of cortical thickness showed significant sex-by-group interactions in the supramarginal gyrus/inferior parietal cortex. However, post hoc tests showed that this was driven by reduced cortical thickness in the left supramarginal gyrus in DBD males compared to HC males, but not for DBD females compared to HC females. The

supramarginal gyrus is consistently implicated in decision making (Silani et al., 2013) and emotion processing (Camacho et al., 2019). Further, parietal regions implicated in memory and attention are recruited during cognitive control processes along with the ventral prefrontal cortex to modulate amygdala reactivity (McRae et al., 2012; Buhle et al., 2014; Silvers et al., 2016). Functional MRI studies also suggest that aberrant activation of parietal regions during executive control tasks is associated with disruptive behaviors (White et al., 2012; Alegria et al., 2016; Klapwijk et al., 2016). Similarly, recent structural imaging work suggests an association between perturbations in parietal regions and greater levels of disruptive behaviors in children (Caldwell et al., 2015). For instance, reductions in cortical thickness of the parietal cortex including the supramarginal gyrus was reported in prior studies of youths with DBD using surface-based morphometry (Hyatt et al., 2012; Jiang et al., 2016; Smaragdi et al., 2017). While we did not have a priori hypotheses related to laterality, in the current study we observed a significant sex-by-group interaction for cortical thickness in the supramarginal gyrus in the left hemisphere, while Smaragdi et al. (2017) observed a sex-by-group interaction in the right hemisphere. Despite these laterality differences, both supramarginal regions reported here and by Smaragdi et al. (2017) are similar and extend into the inferior parietal cortex/angular gyrus. Other studies have also reported reduced cortical thickness in adolescents and young adults with conduct disorders compared to controls in a similar region as the current study in the left supramarginal gyrus/parietal cortex (Hyatt et al., 2012; Jiang et al., 2016). Structural perturbations in parietal regions could also be related to deficits in decision-making and emotion recognition in males with conduct problems (Fairchild et al., 2009a, 2009b). Further, given that temporal and parietal regions are recruited during emotion regulation processes along with the ventral prefrontal cortex to modulate amygdala reactivity (McRae et al., 2012; Buhle et al., 2014; Silvers et al., 2016), it is possible that dysfunction in parietal regions in DBD could disrupt adaptive responding to threat and emotionally salient stimuli.

Our results indicate potential additive effects of sex and group on brain structure in children with DBD for the vmPFC and supramarginal gyrus. While sex-by-group interactions were found for medial prefrontal and parietal regions in this study, it is important to note that this effect was most prominent for boys with DBD, but not girls with DBD in our sample. Therefore, a somewhat cautious interpretation of these results related to sex-specific differences in DBD is merited. Disruptions in cortical thickness and volume could reflect multiple paths to the same outcome (in this case, disruptive behavior), termed "equifinality", in girls and boys. For instance, this could include deviations in brain development, such as gray matter thinning (in boys) vs. increased myelination (in girls), superimposed on sex differences in rates of brain maturation in girls (faster, with gray matter thinning occurring earlier) and boys (slower, with gray matter thinning occurring later) (Giedd et al., 2015). Further, differences in brain development among children with DBD have been reported that might reflect delayed cortical maturation (De Brito et al., 2009; Oostermeijer et al., 2016). It is also possible that these findings of structural perturbations in the vmPFC and supramarginal gyrus could reflect a developmental consequence of the functional and/or structural deficits in the amygdala in DBD, a region consistently implicated in the pathophysiology of disruptive behaviors (Blair et al., 2014, 2016; Rogers and De Brito, 2016) with known reciprocal connections to the prefrontal and parietal regions and well-established roles in emotion regulation (Silvers et al., 2016) and social functioning (McRae et al., 2012).

It is important to note that while there was a significant sex-by-group interaction for gray matter volume in the vmPFC and cortical thickness in the supramarginal gyrus, our results suggest that this may be a result in males with DBD that does not replicate in females with DBD. Thus, given the novelty of these findings in context of the relatively few structural MRI studies investigating sex differences in youths with conduct problems, a cautious interpretation is recommended. It is possible that differences in cortical volume and thickness observed here

for DBD boys compared to HC boys could also indicate disruptions in normative neural developmental processes such as preprogrammed synaptic pruning and myelination (Giedd et al., 2015). Additionally, individual differences in the rate and timing of brain development may be subtle and different for boys and girls with DBD to arrive at similar clinical presentations of disruptive behavior (Gennatas et al., 2017; Kaczkurkin et al., 2019). In support of this, there were no significant differences in the severity of disruptive behavior between DBD boys and DBD girls in the current sample. However, the cross-sectional design of the current study limits inferences about differences in developmental trajectories, which is beyond the scope of this study. Finally, the use of dimensional measures may be more advantageous to assess sex differences in brain structure over categorical or case-control designs in structural MRI research (Kaczkurkin et al., 2019) because they capture the full spectrum of symptoms and may be more representative of the actual presentation of symptoms in the population (Casey et al., 2013, 2014; Insel, 2014; Ibrahim and Sukhodolsky, 2018). Given that neural development can go awry in several ways resulting in disturbances in cognition, affect, and behavior (Shaw et al., 2010), future longitudinal work will be important in order to capture sex-specific underlying structural aberrations in developmental processes in children with disruptive behavior.

Sex-by-CU traits interactions were observed for left amygdala volume in the DBD group: that is, males showed a positive whereas females showed a negative association between CU traits and gray matter volume in the left amygdala after controlling for the shared variance in externalizing behavior. We also found a sex-by-externalizing behavior interaction in the total sample for left vmPFC volume, whereby males showed a negative and females showed a positive association between externalizing behaviors and cortical volume after controlling for the shared variance in CU traits. These findings add to prior studies of youths with DBD reporting associations between disruptive behaviors, CU traits and gray matter volume (Michalska et al., 2015; Raschle et al., 2018), particularly in the amygdala (Cohn et al., 2016; Aghajani et al., 2017; Cardinale et al., 2018) and ventral prefrontal cortex (Fairchild et al., 2011; Spechler et al., 2019). For instance, a recent study showed sex-by-CU traits interactions for gyrification (a composite measure of cortical folding) in prefrontal regions (Smaragdi et al., 2017). In another study, Raschle et al. (2018) reported a sex-by-CU traits interaction for the bilateral insula in typically developing youths, in which boys showed a positive correlation between CU traits and insula volume, but not girls. Our findings of sex-by-externalizing interactions for the vmPFC are also similar to findings from prior work reporting an interaction between sex and disruptive behavior symptoms for gyrification in regions including the insula, fusiform gyrus, and temporal-parietal cortex (Smaragdi et al., 2017). In a whole-brain analysis of cortical thickness in the total sample, we also found an association between severity of externalizing behaviors and cortical thickness in the left ventrolateral prefrontal cortex/orbitofrontal cortex across groups of boys and girls after accounting for suppressor effects. Here, children who had greater severity of externalizing behavior showed reduced cortical thickness in the ventrolateral prefrontal cortex after accounting for the unique variance in CU traits. This finding is in line with a recent study that showed reduced gray matter volume in the ventrolateral prefrontal cortex/orbitofrontal cortex was inversely associated with levels of behavioral dysregulation in youth (Spechler et al., 2019). Other studies have also reported associations between reduced cortical thickness and/or volume in prefrontal regions and increased severity of disruptive behavior symptoms in youths (Fairchild et al., 2011; Dalwani et al., 2015; Michalska et al., 2015; Jiang et al., 2016; Oostermeijer et al., 2016). There is a large body of research implicating the ventral prefrontal/orbitofrontal cortex in emotion regulation (Etkin et al., 2015). Additionally, prior studies have suggested a role of impaired ventral prefrontal/orbitofrontal cortex activation and structure in youths with disruptive behavior (Rubia et al., 2009; Finger et al., 2011; Alegria et al., 2016; Rogers and De Brito, 2016; Sebastian et al., 2016; Aghajani et al., 2017). Together, our findings

from these dimensional analyses add to prior studies suggesting sex-specific relationships between severity of disruptive behavior, CU traits, and brain structure in children (Ducharme et al., 2011; Caldwell et al., 2015; Raschle et al., 2018). Thus, disruptions in structure of the amygdala and prefrontal cortex may play a role in the emergence of disruptive behavior and CU traits. A dimensional approach to model CU traits and disruptive behavior along continua, while simultaneously controlling for suppressor effects, has been used in recent functional (Sebastian et al., 2012; Lozier et al., 2014; Ibrahim et al., 2019) and structural (Sebastian et al., 2016; Cardinale et al., 2018) MRI studies of youth with DBD, and may offer utility in predicting outcomes over and above measures of disruptive behavior (Frick and White, 2008).

We also examined age-related two-way and three-way interactions with sex and group for gray matter volume in the vmPFC and amygdala regions-of-interest, and for cortical thickness in the whole-brain analysis. Despite our hypothesis that the relationship between sex, disruptive behavior, and brain structure might differ with age (Oostermeijer et al., 2016; Bos et al., 2018; Muetzel et al., 2018), no age-related interactions were observed in this study. It is important to note that both of these recent longitudinal structural MRI studies (Oostermeijer et al., 2016; Bos et al., 2018; Muetzel et al., 2018) did not find significant age-related interactions with disruptive behavior in the ventral prefrontal cortex or amygdala. This may suggest that the sex-by-group interactions in the vmPFC and supramarginal gyrus reported here could reflect structural developmental trajectories that are potentially similar for boys and girls with DBD across the age range. While there are emerging studies examining sex differences in brain structure in youths with DBD, future work is needed to test whether there are also sex differences in functional activation between girls and boys with disruptive behavior. Explicitly testing sex-by-group interactions in future functional MRI studies could also clarify whether there is a convergence of neural patterns of sex differences observed in functional and structural MRI studies, which could have clinical implications for characterizing youths with DBD based on neurocognitive vulnerabilities and/or developing sex-specific novel treatments tailored to unique neurocognitive impairments (Baker et al., 2015).

Some limitations of this study should also be considered. First, the sample size was modest for a study of sex differences and the female DBD group was smaller compared to the male DBD group. However, the ratio of males and females in this study is similar to reported estimates of male to female ratios for children with DBD (2−3:1) (Wittchen et al., 2011; Erskine et al., 2013; Demmer et al., 2017). It also demonstrates the challenge in recruiting and scanning an adequate sample of girls with DBD to provide sufficient statistical power to examine sex differences in brain structure. Thus, future studies are needed with larger samples to investigate whether the results reported here can be replicated. Second, age-related interactions were not observed in this study. However, the sample size may have been insufficient to detect age effects. Given the cross-sectional design of the current study, future studies using longitudinal designs are necessary to capture and compare trajectories underlying structural abnormalities in neural development in male and female youth with DBD, and to assess whether the results reported here are stable across development. Third, while the main findings in this study remained significant after controlling for comorbid ADHD and internalizing behaviors, future studies that are designed to explicitly investigate the impact of these comorbidities in DBD would be a valuable and informative approach. For instance, the effects of ADHD can be dissociated by comparing brain structure in children with DBD with and without co-occurring ADHD and including control groups of children with ADHD uncomplicated by disruptive behavior. Finally, the lack of assessment of pubertal development should be noted as a limitation in the current study. Future structural MRI studies are needed with matched groups based on pubertal development in order to reduce the possibility of group or sex differences in brain developmental stages. Additionally, future longitudinal studies will be essential for understanding the effects of puberty on sex differences in brain structure in

DBD as they allow for age and pubertal stage to be more easily differentiated in comparison to cross-sectional structural MRI research (Vijayakumar et al., 2018).

5. Conclusions

This study extends our understanding of sex-specific differences in gray matter volume and cortical thickness in youth with disruptive behavior. The present work provides evidence of distinct structural abnormalities in the vmPFC and supramarginal gyrus in boys and girls with disruptive behavior. Further, we found sex-specific unique associations between severity of disruptive behavior, CU traits, and brain structure in boys and girls with DBD. These findings can inform development of sex-specific neural biomarkers of disruptive behavior disorders.

Declaration of Competing Interest

The authors report no declarations of interest.

Dr. Sukhodolsky receives royalties from Guilford Press for a treatment manual on CBT for anger and aggression in children. Drs. Ibrahim, Kalvin, He, Pelphrey, McCarthy, and Mr. Li report no competing interests.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dcn.2020.100884.

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