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Amygdala–Prefrontal Connectivity in Children with Maladaptive Aggression is Modulated by Social Impairment

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Abstract

Aggressive behavior is common across childhood-onset psychiatric disorders and is associated with impairments in social cognition and communication. The present study examined whether amygdala connectivity and reactivity during face emotion processing in children with maladaptive aggression are moderated by social impairment. This cross-sectional study included a well-characterized transdiagnostic sample of 101 children of age 8–16 years old with clinically significant levels of aggressive behavior and 32 typically developing children without aggressive behavior. Children completed a face emotion perception task of fearful and calm faces during functional magnetic resonance imaging. Aggressive behavior and social functioning were measured by standardized parent ratings. Relative to controls, children with aggressive behavior showed reduced connectivity between the amygdala and the dorsolateral prefrontal cortex (PFC) during implicit emotion processing. In children with aggressive behavior, the association between reduced amygdala–ventrolateral PFC connectivity and greater severity of aggression was moderated by greater social impairment. Amygdala reactivity to fearful faces was also associated with severity of aggressive behavior for children without social deficits but not for children with social deficits. Social impairments entail difficulties in interpreting social cues and enacting socially appropriate responses to frustration or provocation, which increase the propensity for an aggressive response via diminished connectivity between the amygdala and the ventral PFC.

Keywords: amygdala functional connectivity, dorsolateral prefrontal cortex, maladaptive aggression, social impairment, ventral prefrontal cortex

Introduction

Maladaptive aggression is common across childhood-onset psychiatric disorders (Connor et al. 2019) and constitutes one of the main reasons for referral to mental health services (Costello et al. 2014). The causal pathways to childhood aggression involve multiple interacting biological, environmental, and psychosocial risk factors (Tremblay et al. 2018). One influential theory, the social information-processing model, identifies deficits in the detection and interpretation of social cues, as well as in the generation and enactment of socially appropriate responses, as key factors that can lead to maladaptive aggression (Crick and Dodge 1994). For example, children may be more likely to respond aggressively if perceived to be intentionally provoked or mistreated (Ray et al. 2008). This distortion in processing social information—referred to as hostile attribution bias—often leads to increased anger arousal and aggressive behavior (Verhoef et al. 2019). The construct of "aggression" refers to a broad

category of behaviors, which often results in harm to self or others (Tremblay et al. 2018). In children with psychiatric disorders, affective, impulsive aggression—also referred to as reactive aggression—represents one of the most clinically challenging behaviors (Vitiello and Stoff 1997). Aggression is also linked to reduced ability to generate and implement socially appropriate solutions to provocation (Orue et al. 2019), as well as to overall impairments in social functioning (Burke et al. 2014). Children with aggressive behavior also show reduced ability to infer another person's thoughts, intentions, and feelings (Happé and Frith 1996; Oliver et al. 2011; Mandy et al. 2013; Holl et al. 2018; Heleniak and McLaughlin 2020). These social cognitive processes, such as reappraisal of frustrating events and generation of nonaggressive responses to provocations, are also the targets of cognitive–behavioral interventions for childhood aggression (Sukhodolsky et al. 2004; Sukhodolsky, Smith, et al. 2016).

Neuroimaging studies of child aggression have identified deficits in emotion processing and reinforcement-based decision making (Alegria et al. 2016). There is also considerable literature on the neural mechanisms of impaired recognition of distress in others (i.e. affective empathy) in individuals with conduct problems and callous-unemotional (CU) traits (Lockwood et al. 2013; Sethi et al. 2018). However, the effects of social impairments other than the lack of affective empathy on the neural mechanisms of aggression have not been well studied. Given the increasing body of research on the neural circuitry of social dysfunction across psychiatric disorders, understanding brain mechanisms of social cognition in children with aggression can offer new insights into the pathophysiology of this common and impairing behavioral problem. Here, we examine if brain responses to emotional faces measured via functional magnetic resonance imaging (fMRI) and aggression severity are moderated by the degree of social impairment in a transdiagnostic sample of children with aggressive behavior.

Neural Correlates of Implicit Emotion Processing Deficits in Childhood Aggression

Implicit emotional face processing tasks are commonly used to study frontolimbic and frontoparietal networks implicated in both threat processing and social perception (Fusar-Poli et al. 2009; Del Casale et al. 2017). Children with disruptive behavior are reported to show over-reactivity in regions involved in emotion generation including the amygdala and insula (Herpertz et al. 2008; Viding et al. 2012), underactivity in prefrontal regions involved in the cognitive control of emotion including the ventromedial, ventrolateral, and dorsolateral prefrontal cortices (vmPFC, vlPFC, and dlPFC, respectively) (Marsh et al. 2008; Aghajani et al. 2017), and reduced connectivity between the amygdala and prefrontal regions (Marsh et al. 2008; Aghajani et al. 2017; Stoddard et al. 2017; Kryza-Lacombe et al. 2019). Disruptions in frontolimbic circuitry during face perception tasks are also well documented in children with autism spectrum disorder (ASD) (Pelphrey et al. 2007; Vandewouw et al. 2020). Our prior work demonstrated that children with ASD and co-occurring aggression showed reduced amygdala–vlPFC connectivity compared with children with ASD-without-aggression; in addition, weaker amygdala–vlPFC connectivity was associated with greater severity of disruptive behaviors after accounting for the presence of CU traits (Ibrahim et al. 2019). Given the central role of the vlPFC as a hub in social cognitive (Dal Monte et al. 2014) and emotion regulation (Silvers et al. 2016) processes, it is possible that social impairment could moderate the association between perturbed amygdala–vlPFC connectivity and maladaptive aggressive responses to threat and emotionally salient stimuli. Thus, in this study, we hypothesized that amygdala–vlPFC connectivity in children with aggression will be modulated by the severity of social deficits. To

examine the moderating role of social impairment on frontoamygdala connectivity and aggression in youths—which was motivated by prior imaging work of aggressive behavior in ASD (Ibrahim et al. 2019)—we leveraged a well-established continuous measure of social functioning, the Social Responsiveness Scale—Second Edition (SRS-2) (Constantino 2005). We reasoned that the SRS-2 Social Communication and Interaction subscale—which measures social deficits in the domains of social awareness, motivation, communication, and cognition—would approximate social cognitive deficits implicated in childhood aggression. While the SRS was initially developed to measure core ASD social deficits, it has been shown to have transdiagnostic applications in youths and in the general population for assessing social cognitive impairments behaviorally (Cholemkery et al. 2014) and on a neural level in fMRI studies (Baribeau et al. 2019; Lake et al. 2019; Ibrahim, Noble, et al. 2021).

Evaluating a Neurobiological Mechanism of Aggression Modulated by Social Impairment

Examining the moderating effects of social impairments on the neural circuitry of aggressive behavior is important for at least three reasons. First, psychological deficits in social information processing, such as the ability to recognize and interpret social cues, are correlated with aggressive behavior in children (Capage and Watson 2001; Pardini and Frick 2013). Second, the neurocognitive mechanisms of aberrant emotion processing, particularly fearful faces, are implicated in both aggressive behavior and social impairments (Dawel et al. 2012; Pardini and Frick 2013; Moul et al. 2018). Third, there is increased recognition that social cognitive deficits may be shared across psychiatric and developmental disorders (Happé and Frith 2014; Cotter et al. 2018). To this end, the SRS (Constantino 2005) has been used to capture dimensional social constructs in child psychiatric disorders (Uljarević et al. 2019). The SRS has excellent dimensionality in the general population (Constantino and Todd 2003; Wigham et al. 2012) and was recommended by the NIMH workgroup for probing the Research Domain Criteria (RDoC) framework of social processes (NIMH 2016). Of relevance to this study, the SRS was shown to be correlated with cognitive empathy but not with affective empathy in children (Georgiou et al. 2019), and cognitive empathy is rarely tested in neuroimaging studies of aggressive behavior (Sebastian et al. 2012). In this study, the SRS was used in a dimensional analysis of the neural correlates of aggressive behavior to identify relative contributions of social cognitive deficits to the brain mechanisms of aggression.

Our primary aim was to investigate amygdala–prefrontal connectivity in a transdiagnostic sample of children with clinically significant levels of aggressive behavior. Based on the previous research (Marsh et al. 2008; Aghajani et al. 2017), we hypothesized that children with aggressive behavior would show reduced

amygdala–prefrontal connectivity during implicit emotion processing compared with unaffected, healthy controls. Our second aim was to test if the association between the amygdala–prefrontal connectivity and the severity of aggression measured by the Child Behavior Checklist (CBCL) Aggressive Behavior Scale (Achenbach and Rescorla 2001) is moderated by severity of social impairment measured by the SRS-2 Social Communication and Interaction (SCI) subscale (Constantino 2005), as continuous measures of aggressive behavior and social functioning, respectively. These dimensional analyses were conducted in the sample of children with aggression ($n = 101$). In addition, the covariance between social deficits and CU traits was controlled by including the Inventory of Callous-Unemotional (ICU) traits (Frick 2003) score as a covariate. Given the influence of age on amygdala functional connectivity development (Gee et al. 2013; Gabard-Durnam et al. 2014; Gabard-Durnam et al. 2018), we also tested age-related differences between aggressive behavior and healthy control groups. Thus, even though exploratory in nature, we expected younger children versus adolescents with aggression to show distinct patterns of attenuation in amygdala–PFC connectivity relative to healthy controls. The third aim was to investigate amygdala reactivity to fearful faces as a potential transdiagnostic neuromarker of aggressive behavior. Amygdala reactivity to fearful faces has been shown to be increased in children with conduct problems without CU traits and decreased in children with conduct problems and high levels of CU traits (Sebastian et al. 2012; Lozier et al. 2014). Here, we tested if the association of amygdala reactivity to fearful expressions with aggressive behavior is moderated by the severity of social impairment controlling for CU traits. We predicted that amygdala reactivity to fearful faces would be attenuated in socially impaired children with aggression. We also conducted follow-up sensitivity analyses in which we systematically assessed the impact of covariates related to CU traits, co-occurring anxiety, and psychotropic medication use in both amygdala connectivity and region-of-interest (ROI) analyses.

Materials and Methods
Subjects
The sample included 101 children of age 8–16 years old with clinically significant aggressive behavior (28 females) and 32 healthy controls (13 females) without aggressive behavior. Table 1 shows demographic and clinical characteristics of participants. Detailed inclusion and exclusion criteria are provided in the Supplementary Material. Children with aggressive behavior participated in a treatment study of behavior therapy for irritability and aggression (Sukhodolsky, Wyk, et al. 2016), and this paper reports fMRI and clinical characterization data that were collected prior to initiating the treatment. One of the inclusion criteria for the treatment study was a T-score of 65 or greater on the CBCL Aggressive Behavior Scale (Achenbach and Rescorla 2001). In

addition to high levels of aggression on the dimensional measure, all children met criteria for Oppositional Defiant Disorder, Conduct Disorder, or Disruptive Mood Dysregulation Disorder. Children were allowed to have co-occurring psychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD), ASD, and anxiety if the presence of co-occurring disorders did not require immediate treatment. There were no significant differences in aggression severity between girls and boys in the aggressive behavior group ($t_{99} = 0.81$, $P = 0.43$) or in the total sample ($t_{131} = 1.31$, $P = 0.19$). There were also no significant correlations between CBCL aggression severity and gender in the aggressive behavior group ($r = -0.08$, $P = 0.42$) or in the total sample ($r = -0.13$, $P = 0.12$): See the Supplementary Results and Supplementary Table S10 for additional correlations between study variables. Each participant's parent provided informed consent according to the institutional review board at the Yale University School of Medicine. Each child provided verbal and written assent. This study was reviewed and approved by the local ethical committee (institutional review board at the Yale University School of Medicine), and it was conducted in accordance with the declaration of Helsinki.

Clinical Assessment
All 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 Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnoses of Disruptive Behavior Disorders as well as co-occurring psychopathology. ASD diagnosis was confirmed with the *Autism Diagnostic Interview—Revised* (Le Couteur et al. 2003) and *Autism Diagnostic Observation Schedule—Second Edition* (Lord et al. 2012). Full-scale IQ was evaluated with the *Wechsler Abbreviated Scale of Intelligence* (Wechsler 1997). Parents completed demographics and medical history forms.

Parents also completed the CBCL, a well-established measure of child psychopathology (Achenbach and Rescorla 2001). The *CBCL Aggressive Behavior Scale* includes 16 items reflecting inappropriate anger outbursts, as well as verbal and physical aggression. A *T*-score of 65 represents a cutoff for a clinically significant level of aggression. The parent-rated SRS-2 Social Communication and Interaction (SCI) subscale score (53 items are included in the SRS-2 SCI subscale) (Constantino 2005) was used as a dimensional measure of severity of social impairments. The SCI represents four dimensions of social behaviors including social awareness, motivation, communication, and cognition. Higher scores on the SRS-2 SCI indicate greater social impairment. We reasoned that the SCI subscale would approximate deficits in social cognition related to maladaptive aggression. The SRS was initially developed to measure social impairment in ASD but was shown

Table 1. Participant demographics and clinical characteristics

Variable	Children with aggressive behavior, $n = 101$	Typically developing healthy controls, $n = 32$	Total sample, $N = 133$	P value[a]
Age, years (SD)	11.8 (2.2)	12.7 (1.9)	11.9 (2.1)	0.03[b]
Male, %	72.3	59.4	69.2	0.19
Mean IQ[c] (SD)	107 (13.9)	112 (12.3)	107.7 (13.7)	0.07
Race, %				0.37
White	77.2	65.6	74.4	
Black	11.9	21.9	14.3	
American Indian/Alaska native	1.5	0	1.5	
Asian/Pacific Islander	2.0	0	1.5	
Other/more than one race	6.9	12.5	8.3	
Ethnicity				0.48
Hispanic	15.8	12.5	15.0	
Non-Hispanic	84.2	87.5	85.0	
Mean CBCL aggressive behavior T-score (SD)	75.2 (7.5)	50.9 (2.5)	69.4 (12.3)	<0.001[d]
Mean ICU score (SD)	33.2 (9.6)	14.8 (6.4)	28.7 (11.9)	<0.001[d]
Mean SRS-2 SCI T-score	65.4 (11.3)	45.4 (8.6)	60.7 (13.7)	<0.001[d]
DSM-5 diagnoses[e] (n, %)				
Oppositional defiant disorder	81 (80.2)			
Conduct disorder	12 (11.9)			
DBD-NOS	3 (3)			
DMDD	16 (15.8)			
ASD	18 (17.8)			
ADHD	77 (76.2)			
Anxiety disorder	26 (25.7)			
Depressive disorder	4 (4)			
Medication (n, %)	47 (46.5)			
Type of medication (n, %)				
Stimulants	32 (31.7)			
Nonstimulants	20 (19.8)			
Antidepressant	13 (12.9)			
Neuroleptics	13 (12.9)			
Mood stabilizers	4 (4)			
Benzodiazepines	2 (2)			

Notes: ADHD, attention-deficit/hyperactivity disorder; CBCL, Child Behavior Checklist; DMDD, disruptive mood dysregulation disorder; HC, healthy controls; ICU, Inventory of Callous-Unemotional Traits; SRS-2 SCI, Social Responsiveness Scale-Second Edition (SRS-2) Social Communication and Interaction subscale score (SCI). [a]Significant group differences at $P < 0.05$ using Chi-square test for categorical variables or independent samples T-test. [b]HC > Aggressive Behavior group. [c]Full-scale IQ measured by the Wechsler Abbreviated Scale of Intelligence (Wechsler 1997). [d]Aggressive Behavior group > HC. [e]Following DSM-5, oppositional defiant disorder diagnosis was not assigned to children who met criteria for DMDD.

to capture social cognitive impairments in the general population, as well as in children with disruptive behavior disorders (Cholemkery et al. 2014). Parents also completed the ICU (Frick 2003) and the total score was used as a dimensional measure of CU traits.

Dimensional measures of aggression and social impairments were selected to allow comparison with prior fMRI studies. The CBCL aggression-related scales have been extensively used in prior neuroimaging studies with samples of children with disruptive behavior (Lozier et al. 2014; Cardinale et al. 2018; Ibrahim et al. 2019; Ibrahim, Kalvin, et al. 2021). The SRS-2 SCI subscale has also been used in neuroimaging research of children with and without ASD (Baribeau et al. 2019; Lake et al. 2019), and it is designated as a measure of social cognitive impairment in the RDoC social processes domain (Abram et al. 2015; Ibrahim and Sukhodolsky 2018; Clarkson et al. 2020), underscoring its utility in transdiagnostic samples.

Experimental Paradigm

Children completed a block-design fMRI task where they viewed emotionally expressive faces from the NimStim Face Stimulus Set (Tottenham et al. 2009) that depicted fearful and calm expressions with an equal number of male and female faces (Supplementary Fig. 1). The task used a pseudorandomized block design with 12 blocks that each contain two randomly selected faces per block exhibiting the same expression: 6 calm emotion and 6 fearful emotion blocks. The face-expression pair of images were randomly selected throughout the blocks and no individual face-expression image is displayed more than once throughout the paradigm. Each block was 12 s in length and consisted of two faces displayed for 5.5 s each that were separated by a 1-s intertrial fixation cross (i.e., two faces displayed in succession per block with only one face on the screen at a time). Blocks were separated by a jittered interblock interval between 8 and 12 s to optimize statistical efficiency. The interblock intervals were pseudorandomized such that the mean of all interblock intervals was 10 s. The first block was preceded by a 10-s initial fixation cross and the final block was succeeded by an identical 10-s fixation cross. The total duration of the paradigm was 284 s. To ensure attention to the stimuli, participants were instructed to

perform an orthogonal gender identification task using a button press in their left or right hand to indicate male or female, respectively. We examined connectivity across both emotions (fearful and calm) to understand deficits in implicit emotion face processing associated with aggressive behavior and to ensure sufficient continuous voxel time course for psychophysiological interaction (PPI) analyses. For amygdala ROI analyses, to understand differences in amygdala reactivity to threat or fearful faces in children with aggression, fearful versus calm faces was the contrast of interest because the presentation of fearful faces is shown to strongly activate the amygdala (Morris et al. 1996; Fusar-Poli et al. 2009). Additional task details are also reported elsewhere (Sukhodolsky, Wyk, et al. 2016; Ibrahim et al. 2019; Ibrahim, Noble, et al. 2021): Behavioral performance results are reported in Supplementary Table 2. A mock scanner was used to acclimate participants to the scanning environment prior to the fMRI session (see Supplementary Material).

Imaging Acquisition/Preprocessing

Functional MRI data were collected using a Siemens MAGNETOM Tim Trio 3 Tesla 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. For each participant, 137 interleaved, oblique whole-brain functional volumes were collected in the axial plane parallel to the anterior-posterior commissure (AC-PC) line using an EPI gradient echo sequence: TR = 2000 ms; TE = 25 ms; voxel size = 3 × 3 × 4 mm, 34 slices; flip angle = 60°; matrix size = 642; FOV = 2202 mm.

Preprocessing and functional imaging statistical analyses were conducted using the fMRI of the Brain (FMRIB) Software Library (FSL Version 4.1.6; FMRIB, Oxford, United Kingdom) (Smith et al. 2004; Woolrich et al. 2009). Functional data were temporally realigned to correct for interleaved slice acquisition. Motion was corrected using FSL MCFLIRT linear realignment tool (Jenkinson et al. 2002). Eight children with aggressive behavior and one typically developing child were excluded from the final analysis owing to excessive motion (i.e., >3 mm/degrees of motion relative to the first undiscarded volume) and computer error during the scan, respectively. Data were spatially smoothed with a 5-mm full-width at half-maximum isotropic Gaussian kernel with a nonlinear high-pass filter (60-s cutoff). Individual participant analyses were conducted using FSL FMRI Expert Analysis Tool (FEAT). Functional images were registered to coplanar images, which were then registered to the high-resolution T1-weighted images and normalized to the Montreal Neurological Institute 152 template.

Data were corrected for structured noise associated with motion artifacts using the AROMA package (Pruim et al. 2015) (https://github.com/rhr-pruim/ICA-AROMA).

AROMA is an independent component analysis (ICA)-based method that automatically classifies and removes components identified as noise. ICA-AROMA is a robust approach for denoising and removing motion artifact in pediatric fMRI data (Ciric et al. 2017; Gabard-Durnam et al. 2018) and preserving temporal degrees of freedom while eliminating distance-dependent artifact without inducing false anticorrelations (Pruim et al. 2015; Ciric et al. 2017). Noise components were detected and removed prior to any temporal filtering, so the resulting cleaned data were temporally high-pass filtered. At the single-subject level, we also regressed the white-matter time series, which was included as a confound variable in first-level FEAT analyses. No between-group differences were observed in mean head motion (Supplementary Table 1). Additional detail regarding data acquisition and preprocessing is also provided in the Supplementary Methods.

Psychophysiological Interaction Analysis
Categorical Analyses

We first examined differences in amygdala–prefrontal connectivity between the aggressive behavior and the HC groups using a PPI analysis (Friston et al. 1997). Whole-brain PPI tests were conducted across fearful and calm faces. Amygdala ROIs were anatomically defined using the Harvard-Oxford atlas, with a threshold set at ≥25% probability. A general linear model was created that included the following regressors: psychological (task), physiological (amygdala ROI time series), PPI, and nuisance (six motion parameters). We did not have a priori hemispheric hypotheses and therefore analyses were conducted for both the right and the left amygdala. Group-level analyses applied a cluster-forming threshold of $Z > 3.1$ (corresponding to $P < 0.001$) and a whole-brain correction at $P < 0.05$ family-wise error rate-corrected using random field theory. Additional detail of the PPI analysis is provided in the Supplementary Material. Age and IQ were included as covariates in all models. We also investigated age-related differences between the groups (group × age interaction).

Dimensional Analyses

Next, we conducted dimensional PPI analyses in the aggressive behavior group ($n = 101$) to assess whether the association between amygdala connectivity and aggression severity is moderated by severity of social impairments. Severity of aggressive behavior (using the CBCL Aggressive Behavior score) and social impairments (using the SRS-2 SCI score) were modeled as continuous variables to maximize statistical power, with the interaction of CBCL Aggressive Behavior total score × SRS-2 SCI total score. Whole-brain PPI tests were conducted across all emotions and the regression models included IQ and age as covariates. In addition, consistent with prior dimensional fMRI work in children with conduct problems (Lozier et al. 2014; Ibrahim et al. 2019; Ibrahim, Kalvin, et al. 2021), level of CU traits was included as a covariate to identify the unique contribution of

social impairment to predicting amygdala connectivity in children with aggression. To visualize interactions, beta coefficient values averaged from each cluster were extracted for each subject using FSL Featquery and compared across groups in post hoc analyses for ventral PFC regions that emerged as significant and were plotted based on a median split in SRS-2 SCI scores. That is, for hypothesis testing, social impairment was treated as a continuous measure in dimensional PPI analyses. However, when significant associations with amygdala connectivity and aggression were observed, we used a post hoc comparison median split of SRS-2 SCI to illustrate social impairment moderation of amygdala–prefrontal connectivity differences among children with aggression (in the aggression group: $n = 49$ for low social impairment and $n = 52$ for high social impairment). We also investigated interactions with age, social impairment severity, and aggression severity (SRS-2 SCI × CBCL Aggressive Behavior × age interactions).

Amygdala ROI Analyses

To test amygdala reactivity to threat or fearful faces as a potential neurobiological marker of aggressive behavior, as well as moderation by social impairments, we conducted a ROI analysis of amygdala reactivity. Featquery was used to extract beta coefficients of the mean parameter estimate values for the contrast fearful versus calm using bilateral amygdala anatomical ROI masks (described above). The regression models included severity of aggression (using the CBCL Aggressive Behavior score) and social impairments (using the SRS-2 SCI score) modeled as continuous variables, the interaction of CBCL Aggressive Behavior × SRS-2 SCI, and amygdala reactivity to fearful faces as the dependent variable. Regression models included ICU scores, age, and IQ as covariates. Results are plotted according to a median split in SRS-2 SCI scores for visualization.

Exploratory Analysis of Whole-Brain Task Activation

For completeness, we conducted an exploratory whole-brain analysis to test between group differences in task activation during implicit emotion processing for regions not included in our a priori hypothesis. IQ and age were included as covariates. We also tested for age-related differences between the groups (group × age interaction). The identical statistical thresholds were used as mentioned above for the PPI analysis. We provide these findings in detail in the Supplementary Methods and Supplementary Results (Supplementary Table 7 and Supplementary Fig. 3) for the interested reader.

Follow-up Analyses
Potential Covariates

Additional analyses were conducted to test the robustness of significant effects. First, sensitivity analyses were conducted that accounted for CU traits using the ICU total score as well as co-occurring anxiety disorder

diagnosis (0 = no, 1 = yes; based on the K-SADS diagnostic interview) and psychotropic medication use (0 = no, 1 = yes) included as covariates in the models. Sensitivity analyses were conducted by repeating the PPI models that emerged as significant for categorical analyses and dimensional analyses but with CU traits (ICU total score), anxiety disorder diagnosis, and psychotropic medication use included as covariates in the models. To account for co-occurring anxiety, we included anxiety diagnosis as a dichotomous variable. Participants with co-occurring disruptive behavior disorder and anxiety disorder ($n = 26$) met DSM-5 criteria based on a diagnostic interview using the K-SADS for a current comorbid diagnosis of generalized anxiety disorder, social anxiety disorder, separation anxiety disorder, or specific phobia. Anxiety disorder based on DSM-5 diagnosis as a dichotomous variable was used to account for the presence of comorbid anxiety in our transdiagnostic sample (Bubier and Drabick 2009; Dugré et al. 2020; Isdahl-Troye et al. 2021).

Psychotropic Medication Use

Given that psychotropic medications may influence functional brain connectivity (Linke et al. 2017), we examined the effects of medication status in a separate post hoc analysis (beyond using medication status as a covariate) on main connectivity findings. Specifically, we tested whether the main findings retained significance after excluding participants taking psychotropic medications and whether there were connectivity differences between medicated and non-medicated children in the aggression group.

Construct Specificity

Next, to test the construct specificity of prefrontal regions emerging as significant in PPI and ROI analyses in predicting aggression severity, we examined whether amygdala connectivity and reactivity were associated with social impairment and internalizing problems using a standardized continuous measure (CBCL Internalizing Problems × SRS-2 SCI interaction). Post hoc tests were also conducted to assess the robustness of findings using gender as a covariate (males = 0, females = 1) and in a gender-matched sample.

Results
Amygdala Functional Connectivity: Categorical Analyses

First, we examined if there were differential patterns of amygdala functional connectivity between children with aggressive behavior compared with healthy controls. Children with aggressive behavior showed reduced connectivity between the right amygdala and right dlPFC (center of mass: 26.4, 28.1, and 42.4) relative to healthy controls during implicit emotion processing (Fig. 1A). Children with aggressive behavior also showed hyperconnectivity between the right amygdala and two
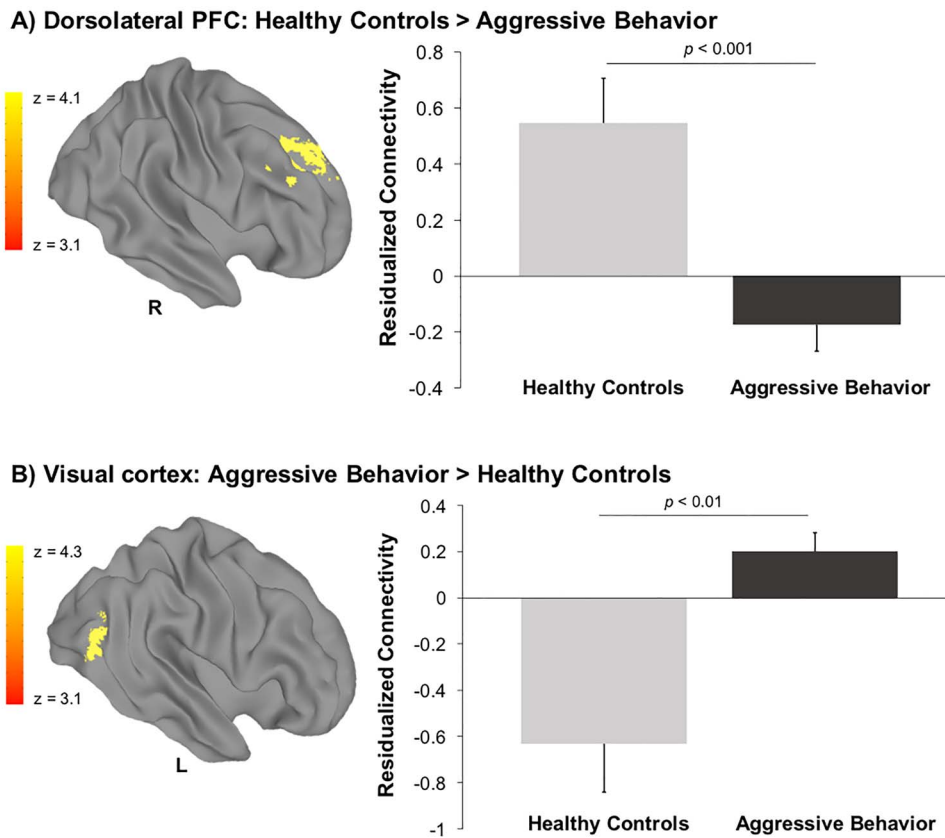
Figure 1. Reduced amygdala–prefrontal connectivity in children with aggressive behavior. Decreased levels of connectivity were observed between the right amygdala and the right dorsolateral prefrontal cortex (PFC) in children with aggressive behavior ($n = 101$) compared with healthy controls ($n = 32$) during implicit emotion processing (A). Hyperconnectivity between the right amygdala and the left visual association cortex was observed for children with aggressive behavior compared with healthy controls (B). Standard error is represented in bar graph error bars. The y-axis shows residualized connectivity strength with age and IQ partialled out.

clusters in the left visual association cortex (center of mass: −41.7, −69.9, 9.1 and −19.3, −46.3, −1) compared with healthy controls (Fig. 1B). Peak coordinates are reported in Supplementary Table 3. Sensitivity analyses were conducted by repeating the main analysis and including potential covariates, which revealed a highly similar pattern of results after accounting for CU traits (using the ICU total score), as well as for anxiety disorder diagnosis and psychotropic medication use (as dichotomously coded variables) (all $Ps < 0.03$) (see Supplementary Results: Sensitivity Analyses). No significant group differences were found for left amygdala connectivity. There were also no significant interactions observed between group and age for either left or right amygdala connectivity.

Exploratory analyses were also conducted to examine connectivity differences in subgroups of children with aggression and low versus high social impairment that were formed based on a median split of a T-score of 65 on SRS-2 SCI subscale (Supplementary Material). We reasoned that this could inform future work in understanding categorical versus RDoC dimensional approaches in characterizing psychopathology, particularly childhood aggression (Parkes et al. 2020). Results of these analyses are provided in the Supplementary Results for the interested reader.

Amygdala Functional Connectivity: Dimensional Analyses

Next, we examined the relationship between amygdala connectivity, aggression severity, and social impairment modeled dimensionally. In the aggressive behavior group ($n = 101$), there was a CBCL Aggressive Behavior × SRS-2 SCI interaction for right amygdala connectivity with a cluster in the right vlPFC (center of mass: 43.1, 27.3, −11.6) during implicit emotion processing (Fig. 2). Specifically, children with higher severity of social impairment showed reductions in right amygdala–vlPFC connectivity with increasing severity of aggression, while children with low severity of social impairment showed the opposite pattern. Peak coordinates are reported in Supplementary Table 4. Sensitivity analyses conducted by repeating the main analysis and controlling for CU traits (ICU total score) as well as co-occurring anxiety disorder diagnosis and medication use (as dichotomous variables) did not alter these findings ($P < 0.01$) (see Supplementary Results: Sensitivity Analyses). No significant associations between social impairment and aggression severity were found for left amygdala connectivity. There were also no significant two-way or three-way interactions observed between social impairment severity, aggressive behavior severity, and age for either left or right amygdala connectivity. We also repeated this

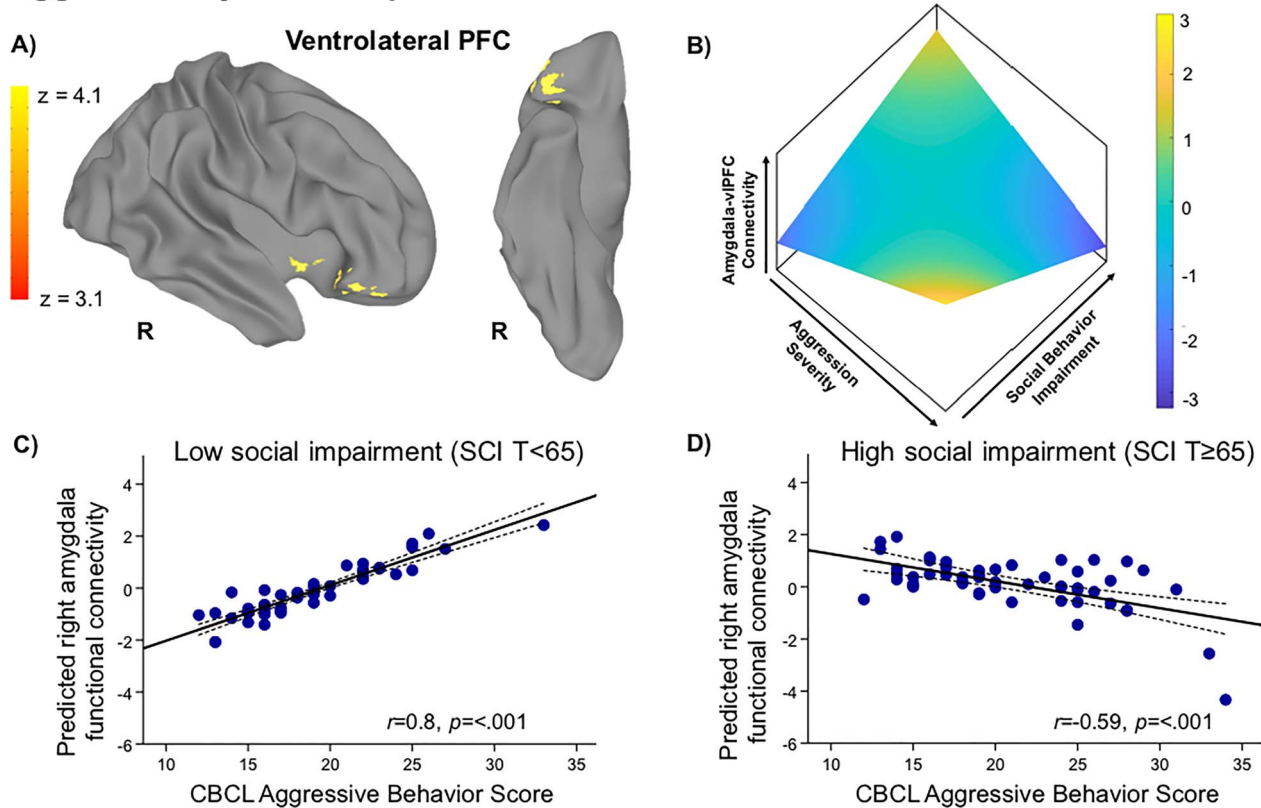## Aggression-by-social impairment interaction

Figure 2. Associations between amygdala–prefrontal connectivity and severity of aggression is modulated by social impairment in youth. In dimensional analyses restricted to the aggressive behavior group ($n = 101$), increasing severity of aggressive behavior and social impairment were associated with reduced connectivity between the right amygdala and the right ventrolateral prefrontal cortex (vlPFC) during implicit emotion processing after accounting for the covariance with CU traits (A). The CBCL Aggressive Behavior Scale score was used as a continuous measure of severity of aggressive behavior and the Social Responsiveness Scale—Second Edition (SRS-2) Social Communication and Interaction (SCI) score was used as a continuous measure of severity of social impairments. A 3D representation is shown for the relationships driving this interaction between the two behavioral dimensions—aggression severity (x-axis) and social impairment severity (y-axis)—and the residuals of the dependent variable amygdala–vlPFC connectivity (z-axis), after adjusting for age, IQ, and CU traits (B). To visualize the interaction effects, mean extracted values for the significant vlPFC cluster are plotted separately by severity of social impairment using a median split T-score of 65 on the SRS-2 SCI subscale to form low social impairment ($n = 49$) (C) and high social impairment ($n = 52$) (D) subgroups. The y-axis represents predicted connectivity strength with the effects of age, IQ, and CU traits partialled out.

analysis in the total sample ($N = 133$), which revealed a similar pattern of amygdala–PFC connectivity, and report findings in Supplementary Table 9 and Supplementary Figure 5 for the interested reader.

Amygdala Activation: ROI Analyses

We then examined whether amygdala reactivity to threat or fear was modulated by social impairment in children with aggression. In the aggressive behavior group ($n = 101$), regression analyses revealed a significant CBCL Aggressive Behavior × SRS-2 SCI interaction for right amygdala reactivity to fearful versus calm faces after accounting for age, IQ, and CU traits ($\beta = -1.1$, $t = -2.1$, $P = 0.04$; Fig. 3). Specifically, in children with low severity of social impairment, right amygdala reactivity to fear was positively associated with aggression severity, but no significant association was found for children with high severity of social impairment. Sensitivity analyses in which the main analyses were repeated controlling for co-occurring anxiety disorder diagnosis and medication

use (as dichotomous variables) did not alter these findings, and these variables did not make significant independent contributions to the variance in amygdala reactivity to fearful faces ($P = 0.5$ and $P = 0.8$ for anxiety and medication, respectively). There was no significant CBCL Aggressive Behavior × SRS-2 SCI interaction for left amygdala reactivity to fear ($P = 0.13$). We also repeated this analysis in the total sample ($N = 133$) and report findings in the Supplementary Results. Mean beta coefficients for the bilateral amygdala ROIs are also show in Supplementary Figure 6.

Follow-up Analyses
Psychotropic Medication Use

As a check on our connectivity findings, we found that after excluding subjects taking psychotropic medications, connectivity findings remained significant for both the right amygdala–dlPFC cluster (in analyses comparing the group of 54 children with aggressive behavior who were not taking medication to 32 healthy controls)

Amygdala reactivity to fearful faces
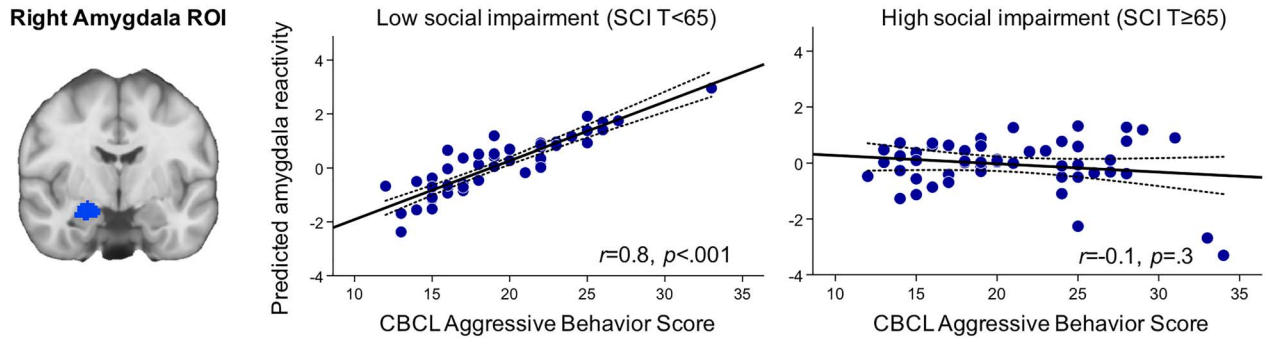
Right Amygdala ROI

Figure 3. Amygdala reactivity to fearful faces is associated with severity of aggressive behavior in youth. In the aggressive behavior group ($n = 101$), results of regression analyses revealed a significant CBCL Aggressive Behavior × SRS-2 SCI interaction for right amygdala reactivity to fearful versus calm faces. That is, right amygdala reactivity to fearful faces was associated with severity of aggressive behavior for children with aggression without social deficits ($\beta = -1.1$, $t = -2.1$, $P = 0.04$) but not for children with aggression with social deficits ($P > 0.1$) after controlling for age, IQ, and CU traits. The x-axis shows CBCL Aggressive Behavior Scale scores, which was used as a continuous measure of severity of aggression. The y-axis shows residualized amygdala reactivity with age, IQ, and CU traits partialled out. The left panel shows the right amygdala region-of-interest, which was structurally defined using the Harvard-Oxford atlas in FSL. For visualization, scatterplots display a median split using a T-score of 65 on the SRS-2 SCI subscale.

and the right amygdala–vlPFC cluster (in dimensional analyses conducted in the group of 54 children with aggressive behavior who were not taking medication) (see Supplementary Fig. 4 and Supplementary Table 8).

Next, we tested for any amygdala connectivity differences between medicated and non-medicated subjects in the aggressive behavior group (47 taking psychotropic medications and 54 not taking psychotropic medications). There were no significant differences in connectivity observed between medicated and non-medicated subjects ($n = 47$ taking psychotropic medications; and $n = 54$ non-medicated) for either right or left amygdala connectivity (i.e. null maps). There were also no significant differences in task activation between medicated and non-medicated subjects (i.e. null maps) in the aggressive behavior group.

Construct Specificity

We then further assessed the construct specificity of the association between aggression severity, social impairment, and amygdala connectivity and reactivity. We tested whether regions emerging as significant in dimensional analyses (i.e. right vlPFC in Fig. 2; right amygdala in Fig. 3) predicted a CBCL Internalizing Problems × SRS-2 SCI interaction. For dimensional analyses in the aggression group ($n = 101$), even when social impairment moderated the association between right amygdala–vlPFC connectivity and aggression (Fig. 2), amygdala connectivity to this vlPFC region did not predict a CBCL Internalizing Problems × SRS-2 SCI interaction (i.e. null maps). For ROI analyses in the aggression group (Fig. 3), right amygdala reactivity did not predict a CBCL Internalizing Problems × SRS-2 SCI interaction ($\beta = -0.56$, $t = -1.4$, $P = 0.14$).

We also tested whether findings for amygdala connectivity and reactivity remained significant after accounting for gender as a dichotomous variable ($0 = $male, $1 = $female). The pattern of findings did not change

when including gender as a covariate for all analyses: amygdala–dlPFC cluster in categorical analyses (center of mass: 26.4, 28, 42.4, $z = 4.2$, $P = 1.55$E-08), amygdala–vlPFC cluster in dimensional analyses in the aggression group (center of mass: 44.9, 33.5, -12.8, $z = 3.5$, $P = 0.004$), or right amygdala reactivity in ROI analyses in the aggression group ($\beta = -1.1$, $t = -2.0$, $P = 0.04$).

As a more robust check on these main findings for potential effects of gender, analyses were then repeated in a gender-matched subgroup of children with aggression ($n = 59$). Gender-matched analyses resulted in a pattern of findings that were highly similar to those reported above for right amygdala–dlPFC connectivity (center of mass: 28.2, 26, 43) in categorical analyses as well as right amygdala–vlPFC connectivity (center of mass: 41.8, 21.6, -12.2) and right amygdala reactivity ($\beta = -1.4$, $t = -2.3$, $P = 0.02$) for the CBCL Aggressive Behavior × SRS-2 SCI interactions in the aggression group. Significant PPI clusters are reported in the Supplementary Results (Supplementary Table 5).

Follow-up Analyses for Sex Differences in Amygdala Connectivity

To facilitate comparisons with prior research examining sex differences in brain structure in children with aggressive behavior (Smaragdi et al. 2017; Ibrahim, Kalvin, et al. 2021), PPI analyses of amygdala connectivity were also conducted to test for the interaction between sex and group (healthy controls, aggressive behavior). A sex × group interaction was observed for connectivity between the left amygdala and the bilateral supramarginal gyrus (right hemisphere center of mass: 50.1, -47.4, 44.8, $z = 4.7$, $P = 0.0007$; left hemisphere center of mass: -53.2, -45.4, 46.5, $z = 3.9$, $P = 0.002$); that is, boys with aggression showed decreased amygdala–supramarginal gyrus connectivity, but girls with aggression showed the opposite pattern relative to respective control groups. We describe these findings in detail in

the Supplementary Results, Supplementary Table 6, and Supplementary Figure 2 for the interested reader.

Discussion

This study examined interactions among aggression, social impairment, and amygdala–prefrontal connectivity in a transdiagnostic sample of children with aggressive behavior. Three key findings emerged. First, during implicit emotion processing, children with aggressive behavior showed reduced amygdala–PFC connectivity. Specifically, decreased amygdala–dlPFC connectivity was observed in children with aggressive behavior during implicit emotion processing compared with controls. Second, amygdala–prefrontal connectivity varied by both severity of aggression and social impairment in children with aggressive behavior. That is, during the processing of emotional faces, children with lower severity of social impairment showed a positive correlation between right amygdala–vlPFC connectivity and severity of aggression, while children with high severity of social impairments showed a negative correlation between right amygdala–vlPFC connectivity and severity of aggression. Third, the association between amygdala reactivity to fearful faces and severity of aggression was moderated by the severity of social impairment in children with aggressive behavior. Follow-up tests revealed that this association was present in children with aggressive behavior without social impairments, but not in children with both aggressive behavior and social impairment. These networks and regions (i.e., amygdala–dlPFC, amygdala–vlPFC, and right amygdala reactivity) also emerged as consistently robust in sensitivity analyses despite co-occurring internalizing symptoms, gender, and psychotropic medication use. Consistent with prior work, these findings demonstrate disruptions in amygdala reactivity and connectivity in youth with aggressive behavior (Lozier et al. 2014; Aghajani et al. 2017; Cardinale et al. 2018; Ibrahim et al. 2019). This study also demonstrates for the first time that the association of aggression with amygdala–prefrontal connectivity and amygdala reactivity is moderated by social cognitive deficits. These findings lend neurobiological support to the social information processing model of aggression—which posits that deficits in the detection and interpretation of social cues, as well as in the generation and enactment of socially appropriate responses can lead to maladaptive aggression (Crick and Dodge 1994)—in the context of aberrant frontolimbic coupling that is moderated by social deficits in children with aggression.

Consistent with prior research, children with aggressive behavior relative to unaffected controls evidenced reduced amygdala–dlPFC connectivity during the processing of emotional faces (Marsh et al. 2008; Ibrahim et al. 2019). Thus, reduced amygdala–prefrontal connectivity represents one of the few consistent and replicable findings in research on aggressive behavior using face emotion processing tasks. A recent study of pediatric

irritability, a construct similar to maladaptive aggression, also reported reduced connectivity between the right amygdala and left dlPFC when processing fearful faces (Kryza-Lacombe et al. 2019). Despite the laterality differences observed in amygdala–dlPFC connectivity between the current study and Kryza-Lacombe et al. (2019) (left vs. right dlPFC, respectively), the connectivity findings were similar and in comparable middle/superior frontal cortex regions spanning the dlPFC. The dorsal and ventral PFC primarily connects to parietal and limbic regions, such as the amygdala, forming a frontoparietal and frontolimbic network that is tightly coupled with the cognitive control of emotion (Etkin et al. 2011). Therefore, projections between the amygdala and the dorsal and ventral PFC are critical in dampening the experience and expression of negatively valenced emotions (Milad and Quirk 2002; Silvers et al. 2016). In addition, amygdala–dlPFC connectivity represents a specific sub-network implicated in emotion regulation (e.g. reappraisal), which involves a conscious effort or the active monitoring of emotion, and thus self-awareness. Our findings show group differences in amygdala–dlPFC connectivity in a transdiagnostic sample of children with aggression relative to children without aggression. Exploratory analyses suggested that there were no differences in amygdala–dlPFC connectivity between subgroups of aggressive children with and without social deficits. Furthermore, recent meta-analytic work also implicates aberrant right dlPFC activation in aggression, particularly related to emotion/threat processing and social cognitive processes (Dugré et al. 2020). Thus, reduced amygdala–dlPFC connectivity may index a transdiagnostic vulnerability for maladaptive aggression regardless of the presence of social deficits.

This study is the first to show that severity of social impairment moderates the association between amygdala–prefrontal connectivity and aggressive behavior. Specifically, in children with aggression with social impairment, greater severity of aggression was associated with reduced amygdala–vlPFC connectivity. However, children with aggression without social impairment showed the opposite pattern (i.e. greater severity of aggression was associated with greater amygdala–vlPFC connectivity). In addition, social deficits indexed by the SRS-2 SCI moderated the association of amygdala–vlPFC connectivity with aggression severity even after controlling for CU traits. The vlPFC is involved in social perception and emotion processing, including higher-order social cognition referred to as theory of mind (Fusar-Poli et al. 2009; Dal Monte et al. 2014). Behavioral studies show that impairments in emotion recognition and theory of mind are associated with aggressive behavior in children (Capage and Watson 2001; Mandy et al. 2013). Reduced vlPFC and prefrontal activation during social perception tasks is also reported in youth with conduct problems relative to controls (Sebastian et al. 2012; Alegria et al. 2016). We speculate that in aggressive children without social impairment, heightened amygdala–vlPFC connectivity may subserve

social processing distortions, such as hostile attribution bias or rumination on slights and snubs. In other words, there may be recruitment of social cognitive circuitry for the generation of hostile or maladaptive thoughts, which, in turn, can contribute to aggressive actions. In contrast, in children with aggressive behavior and social impairment, there was a significant negative association between amygdala–vlPFC connectivity and aggression severity. We argue that attenuated amygdala–vlPFC connectivity in this high social impairment subgroup may represent a deficit, or lack of social cognitive skills rather than a distortion of social processing. In other words, it is possible that children in this high social impairment subgroup may not be "registering" the social context when they react aggressively to frustration or provocation. In support of this, Dugré et al. (2020) reported disruptions in lateral PFC regions, including the right vlPFC, during social cognitive and cognitive control processes in individuals with aggression. When dimensional analyses were repeated in the total sample ($N = 133$) that combined children in the aggression group and HC children, we found a highly similar pattern in which social impairment moderated the association between aggressive behavior and amygdala–PFC connectivity (that included the dorsomedial PFC and orbitofrontal cortex/vlPFC regions). There were differences with laterality in which left and right amygdala–PFC connectivity emerged as significant in the total sample and aggression group, respectively. These laterality differences may be attributed to the distribution of aggressive behavior and social impairment severity scores when combining samples of healthy controls and children with high levels of aggressive behavior. In addition, amygdala lateralization remains poorly understood despite some evidence to suggest that the right amygdala may be implicated in emotionally arousing stimuli while the left amygdala may be implicated in emotion processing involving cognitive and perceptual processes (Wright et al. 2001; Gläscher and Adolphs 2003). Importantly, similar key regions of the PFC (i.e., dorsomedial PFC and orbitofrontal cortex/vlPFC) involved in emotion regulation and in conduct problems in youths (Alegria et al. 2016) as well as adults (Deming and Koenigs 2020; Dugré and Potvin 2021) emerged as significant in both models, which emphasizes the relationship between aggression severity and amygdala–PFC connectivity in heterogeneous as well as clinical samples. However, caution is warranted when interpreting these findings that were based on moderation analyses of social impairment. Future work is needed to examine mediation models as well as longitudinal studies to test a causal link between social information processing, disrupted frontolimbic connectivity, and increased aggression in youths.

Amygdala ROI analyses of task activation revealed that right amygdala reactivity to threat or fearful faces was positively associated with aggression severity in children with aggressive behavior without social deficits, but not in children with aggressive behavior with social deficits after accounting for CU traits. Thus, the presence of social deficits measured by the SRS-2 SCI dampened amygdala reactivity to fearful faces. In categorical analyses, no significant between group differences were found for amygdala activation (Supplementary Fig. 4). These findings are consistent with prior studies of youth with conduct problems versus healthy controls (Lozier et al. 2014) and a related construct of irritability (Kryza-Lacombe et al. 2019). In addition, aberrant amygdala activation, particularly in the right hemisphere, has been implicated in conduct problems in children (Sebastian et al. 2012; Lozier et al. 2014; Ibrahim et al. 2019) and adults (Poeppl et al. 2019). Here, we also showed that this association between amygdala reactivity and aggression was only significant in aggressive children without social deficits, which could be important for identifying subgroups of children with aggression likely to respond to a particular treatment approach. Amygdala reactivity may also play a role in shaping connectivity between the amygdala and the PFC. For instance, individual differences in amygdala reactivity may influence the maturation of connectivity patterns or reciprocal functional connections between the amygdala and other regions important for cognitive control, potentially placing a child at greater or lesser risk for aggression psychopathology. Longitudinal studies of frontolimbic connectivity during the key periods of socioemotional development are needed to examine how changes in amygdala–PFC connectivity may affect developmental trajectories of child aggressive behavior.

Study Limitations

First, the cross-sectional design of this study was a fundamental limitation, although findings may guide future longitudinal research. Second, the amygdala has distinct subregions, including the basolateral, superficial, and centromedial regions, with structurally and functionally distinct subnuclei that have different patterns of connectivity with prefrontal networks (Aghajani et al. 2017). Investigation of amygdala subregional connectivity was not part of our initial hypotheses and beyond the scope of the current study. However, future work is needed to understand whether differential connectivity with amygdala subregions is associated with severity of aggression and social impairments. Third, this study consisted of predominately boys, and it will be important to investigate sex differences in the functional neural architecture of aggression. However, it is important to note that the ratio of males to females in the current study is similar to reported estimates of male to female ratios for children with disruptive behavior disorders (2–3:1) (Wittchen et al. 2011; Erskine et al. 2013; Demmer et al. 2017). This also illustrates a common challenge in recruiting and scanning a sufficiently sized sample of girls with clinically significant levels of aggression or disruptive behavior disorders, particularly to provide the necessary statistical power to examine sex differences

in brain connectivity. Future studies that leverage large-scale data sets will also provide an ideal opportunity to clarify associations among sex, network connectivity, and aggressive behavior in youths. Fourth, because of the task acquisition length, examining connectivity for emotion contrasts (e.g., fearful vs. calm) would have resulted in an exceedingly short time course for robust connectivity analyses. Thus, it will be important for future studies of aggression in youths to acquire an fMRI acquisition length sufficient for examining network connectivity across and between specific emotion domains. Lastly, because the current study focused on aggression measured by the CBCL Aggressive Behavior subscale, which reflects mostly the reactive aggression construct and irritability/anger, the results of this study may not generalize to youths with more proactive forms of aggressive behavior or serious conduct problems. Given that some studies have suggested distinct neural correlates of reactive and proactive forms of aggression (Naaijen et al. 2020; Werhahn et al. 2020), future studies will be important to elucidate shared and unique patterns of network connectivity implicated in subtypes of aggression during implicit emotion processing. It will also be important to understand the difference in neural mechanisms of behavioral difficulties, such as anger outbursts and reactive aggression, in children seeking outpatient treatment for these behaviors versus neural mechanisms of severe conduct disorder or juvenile delinquency as seen in forensic samples.

Conclusion

Children with aggressive behavior showed reduced amygdala–dlPFC connectivity relative to unaffected controls. Social deficits moderated the association between aggression severity and amygdala–vlPFC connectivity during implicit emotion processing. In addition, increased amygdala reactivity to fearful faces was observed in children with aggression without social deficits, but not in children with aggression with social deficits. These results have implications for neurobiologically defined subgroups of children with aggressive behavior.

Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

Data Availability

To promote data transparency, anonymized data will be available upon reasonable request. Data from the study reported in this paper has also been shared on the National Institute of Mental Health Data Archive (NDA; https://nda.nih.gov/).

Notes

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