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Looming Threats and Animacy: Reduced Responsiveness in Youth with Disrupted Behavior Disorders

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Abstract Theoretical models have implicated amygdala dysfunction in the development of Disruptive Behavior Disorders (DBDs; Conduct Disorder/Oppositional Defiant Disorder). Amygdala dysfunction impacts valence evaluation/response selection and emotion attention in youth with DBDs, particularly in those with elevated callous-unemotional (CU) traits. However, amygdala responsiveness during social cognition and the responsiveness of the acute threat circuitry (amygdala/periaqueductal gray) in youth with DBDs have been less well-examined, particularly with reference to CU traits. 31 youth with DBDs and 27 typically developing youth (IQ, age and gender-matched) completed a threat paradigm during fMRI where animate and inanimate, threatening and neutral stimuli appeared to loom towards or recede from participants. Reduced responsiveness to threat variables, including visual threats and encroaching stimuli, was observed within acute threat circuitry and temporal, lateral frontal and parietal cortices in youth with DBDs. This reduced responsiveness, at least with respect to the looming variable, was modulated by CU traits. Reduced responsiveness to animacy information was also observed within temporal, lateral frontal and parietal cortices, but not within amygdala. Reduced responsiveness to animacy information as a function of CU traits was observed in PCC, though not within the amygdala. Reduced threat responsiveness may contribute to risk taking and impulsivity in youth with DBDs, particularly those with high levels of CU traits. Future work will need to examine the degree to which this reduced response to animacy is independent of amygdala dysfunction in youth with DBDs and what role PCC might play in the dysfunctional social cognition observed in youth with high levels of CU traits.

Keywords Disruptive behavior disorders · Conduct disorder · Oppositional defiant disorder · Amygdala · Threat · Animacy

Disruptive Behavior Disorders (DBDs), which include Conduct Disorder and Oppositional Defiant Disorder, comprise a large proportion of referrals to child and adolescent mental health clinics (Kazdin 2000). Youth with DBDs are at increased risk for antisocial behavior, including violence and aggression (Frick et al. 2005). Notably, psychopathology persists into adulthood for a large proportion of these youth (Fergusson et al. 2010; Robins 1966) at great expense to society (Cohen 1998). Theoretical models of DBDs have implicated amygdala dysfunction in the development of these disorders (see Blair et al. 2014).

The amygdala shows considerable interconnectivity with many cortical and subcortical structures and is implicated in a variety of functional processes. A critical role is in stimulus-reinforcement learning (Davis and Whalen 2001; Everitt et al. 2003). This learning allows an individual to learn the

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"goodness" or "badness" of stimuli and other information relevant to the salience of different aspects of the environment (Uddin 2015). In assigning value to stimuli, the amygdala has been shown to preferentially respond to emotional relative to non-emotional stimuli (e.g. Davis and Whalen 2001; LeDoux 2012). Through its interactions with other structures it is involved in at least four different functional processes. For example, the amygdala has a role in: (i) valence evaluation and response selection through its interactions with ventromedial prefrontal cortex (vmPFC; Knutson and Cooper 2005); (ii) emotional attention through its interactions with temporal and posterior cingulate cortices (PCC; Pearson et al. 2011; Pessoa and Ungerleider 2004); (iii) social cognition as a function of its responsiveness to animacy information (Beauchamp et al. 2003; Cao et al. 2014; Coker-Appiah et al. 2013; Martin 2007; Wheatley et al. 2007); and (iv) the acute threat response, through its interaction with periaqueductal gray (PAG; Gregg and Siegel 2001; Nelson and Trainor 2007; Panksepp 1998).

Amygdala dysfunction has been implicated in the neuropathology of DBD, though the nature of this dysfunction may vary in association with the individual's level of callous-unemotional (CU; e.g. lack of guilt and empathy) traits (Blair et al. 2014). The amygdala's role in stimulus-reinforcement learning has been shown to be compromised in youth with DBDs in the context of aversive conditioning paradigms (Cohn et al. 2013, 2016; Fairchild et al. 2010, 2008). Moreover, increased levels of CU traits are associated with reduced amygdala responsiveness during aversive conditioning (Cohn et al. 2013). With respect to the four functional processes mentioned above, youth with DBDs appear compromised in valence evaluation and response selection at least in the context of moral judgment tasks (this is particularly seen for those with DBDs and heightened CU traits; Harenski et al. 2014; Marsh et al. 2011). In addition, considerable work indicates that youth with DBDs show reduced amygdala responses to emotional stimuli (Jones et al. 2009; Lozier et al. 2014; Marsh et al. 2008; Passamonti et al. 2010; Viding et al. 2012; White et al. 2012a). This reduced amygdala responsiveness to emotional stimuli may be particularly low in youth with CU traits (Lozier et al. 2014; Viding et al. 2012; White et al. 2012a). Notably, youth with DBDs show indications of reduced emotional attention behaviorally (Kimonis et al. 2006; Sharp et al. 2006). In addition, youth with DBDs show reduced activity within temporal cortex (White et al. 2012a), attentional regions (lateral frontal, parietal and posterior cingulate cortices; White et al. 2012b) and response control regions (aIC and iFG; Hwang et al. 2016) during emotion attention paradigms. In short, previous literature indicates that amygdala dysfunction impacts valence evaluation/ response selection and emotion attention in youth with DBDs and is particularly clear in those with elevated CU traits (for reviews see Blair 2013; Blair et al. 2014). However, amygdala responsiveness during social cognition and the responsiveness of the systems making up the acute threat response in youth with DBDs have been less well-examined (though there has been one report of reduced amygdala responses as a function of CU trait level in youth with disruptive behavior during an affective empathy task; Sebastian et al. 2012).

The processing of animacy information is critical for social cognition (Cross et al. 2016). The amygdala preferentially responds to animate relative to inanimate stimuli (Beauchamp et al. 2003; Cao et al. 2014; Coker-Appiah et al. 2013; Wheatley et al. 2007). It has been argued that this preferential amygdala response is critical in the recognition of social-affective stimuli and engaging social processing networks (including lateral temporal cortex, medial prefrontal cortex and temporal-parietal junction; for a review see Ochsner 2008). Indeed, patients with Autism, a developmental disorder associated with impairment in social cognition and behavior (American Psychiatric Association 2013), show disrupted connectivity between amygdala and social processing networks (Weisberg et al. 2014). Youth with DBDs, particularly those with high levels of CU traits, show impaired social cognition and behavior. Youth with DBDs report friendships characterized by conflict and perceptions about the quality of relationships that are markedly different from their peers (Muñoz et al. 2008). Youth high on CU traits also report reduced caring about long-term friendships and relationships (Baird 2002) and asocial behaviors, such as failing to endorse deriving pleasure from emotional connectedness to others (Foulkes et al. 2014).

The amygdala also plays a critical role in a more hierarchical system that mediates acute threat response. The mammalian response to threat is graded: mild, distant threats induce freezing, moderate, somewhat proximal threats induce flight and intense, highly proximal threats induce a reactive aggression response (Blanchard et al. 1977). This response is mediated by an acute threat circuitry, initially identified in animals (Anderson 2012; Falkner and Lin 2014; Gregg and Siegel 2001; Panksepp 1998), running from the amygdala to the PAG via the hypothalamus. Notably, strong stimulation of the PAG in rodents elicits reactive aggressive behavior (Mos et al. 1982). This amygdala-PAG network, responsive to acute threat, has also been identified in humans (e.g. Coker-Appiah et al. 2013; Mobbs et al. 2007, 2010). As noted above, there is ample evidence that the amygdala-vmPFC and amygdala-temporal cortex networks are disrupted in youth with CD (cf. Blair 2013). However, there have been no previous investigations of the amygdala-PAG network. Critically, a core variable for responsiveness of the amygdala-PAG mediated acute threat response is threat proximity (Blanchard et al. 1977). This has been confirmed in human fMRI by simulating increasing proximity via increasing a stimulus' visual angle (closer stimuli take up a greater amount of visual angle; Coker-Appiah et al. 2013). Youth with DBDs are at elevated risk for displaying reactive aggression (Frick and Dickens

2006; Moffitt et al. 2002). This might reflect suggestions that some youth with DBDs might show heightened acute threat responsiveness (leading to an increased probability of responding to threat with aggression rather than freezing or avoidance behavior; Crowe and Blair 2008). Indeed, there have been some reports that youth with DBDs and low CU traits show increased responses, at least within the amygdala, to threat stimuli (Hwang et al. 2016; Viding et al. 2012). A secondary goal of the current paper was to determine the responsiveness of youth with DBDs within acute threat circuitry (amygdala *and* PAG) to core threat variables.

The goal of the current study was to determine, in youth with DBDs, responsiveness to core threat variables (visual threats and encroaching stimuli) and animacy information. In addition, we wished to determine the extent to which this responsiveness varies with level of CU traits. We predicted that: First, youth with DBDs, relative to TD youth, would show reduced responses to negative relative to neutral images, looming relative to receding stimuli and animate relative to inanimate stimuli within the amygdala, PAG (negative relative to neutral/looming relative to receding only) and connected cortical regions (specifically, temporal, lateral frontal and parietal cortices). Second, within the youth with DBDs, CU traits would be inversely associated with responsiveness to looming, negative and animate stimuli within the amygdala, PAG (negative relative to neutral/looming relative to receding only) and connected cortical regions (specifically, temporal, lateral frontal and parietal cortices).

Methods

Participants

The final sample included 58 youth: 31 youth with DBDs and 27 typically developing (TD) youth aged 10 to 17 (Table S1). Data from 3 youth with DBDs were excluded (1 due to movement, 2 for response to less than 75% of trials). Using the smallest observed effect size from previous work (Cohen's d = 1.01 to 2.72; Coker-Appiah et al. 2013), a power analysis was conducted utilizing the G*Power program (Faul et al. 2007). The power analysis revealed that a sample of 58 was sufficient to detect an effect of Cohen's d = .43 and that a sample size of 31 was sufficient to detect an effect of Cohen's d = 1.36. Youth were recruited from the community through advertising and referrals from area mental health practitioners. A statement of informed assent and consent was obtained from participating children and parents. The National Institute of Mental Health Combined Neuroscience Institutional Review Board approved this study.

All youth and parents completed Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS; Kaufman et al. 1997) assessments conducted by a doctoral-level clinician as part of a comprehensive psychiatric and psychological assessment. The K-SADS has demonstrated good validity and inter-rater reliability (kappa >0.75 for all diagnoses; Kaufman et al. 1997). IQ was assessed with the Wechsler Abbreviated Scale of Intelligence (two-subtest form). Exclusion criteria were pervasive developmental disorder, Tourette's syndrome, lifetime history of psychosis, depression, bipolar disorder, generalized, social or separation anxiety disorder, PTSD, neurologic disorder, history of head trauma, history of substance dependence, and IQ < 70. In addition, parents completed the Inventory of Callous-Unemotional Traits (Frick 2004), a measure of callous-unemotional traits. Youth meeting K-SADS criteria for Conduct Disorder or Oppositional Defiant Disorder were included in the DBD group, while comparison subjects did not meet criteria for any K-SAD diagnosis. The groups did not differ significantly on IQ [DBD Mean = 97.87 (SD = 10.86), TD Mean = 101.96 (SD = 12.06); t = .64, p = .53], age [DBD Mean = 14.55 (SD = 2.17), TD Mean = 14.91 (SD = 2.02); t = 1.36, p = .18], or in terms of racial [χ^2 = 6.03, p = .30] and gender [χ^2 = 2.24, p = .13] breakdown. Youth with DBDs had significantly greater levels of CU traits [DBD Mean = 42.81 (SD = 8.50), TD Mean = 12.82 (SD = 23.24); t = 6.70, p < .01] and reactive aggression compared to TD youth [DBD Mean = 4.48 (SD = 1.77), TD Mean = 0.47 (SD = .080); t = 8.85, p < .01]. Of the youth with DBDs, 16 also met criteria for Attention-Deficit/Hyperactivity Disorder and 5 youth were taking medication that could not be withheld during scanning (see Supplementary Table S1 for more detail).

Study Measures

Inventory of Callous-Unemotional Traits (ICU; Frick 2004) The ICU is a 24-item self-report scale designed to assess CU traits in youth. The ICU was derived from the CU scale of the Antisocial Process Screening Device (Frick and Hare 2001) that has been widely used in various youth samples. The construct validity of the ICU has been supported in community and juvenile justice samples (Essau et al. 2006; Kimonis et al. 2008; Lawing et al. 2010).

The Looming Task The looming task involved the presentation of four different types of images: (i) threatening and animate (e.g. snarling dogs); (ii) threatening and inanimate (e.g. pointed gun); (iii) neutral and animate (e.g. sitting rabbit); or neutral and inanimate (e.g. a mug). All animate stimuli were animals and all inanimate stimuli were objects presented on their own (i.e., no hand was holding the gun/mug); for image details, see (Yang et al. 2012). This task has been previous show to elicit activation from the acute threat circuitry and interconnected regions in healthy controls (Coker-Appiah et al. 2013).

Each trial involved the *rapid presentation of the same image 4 times* (250 ms per presentation). Each presentation involved the image taking up a greater (or lesser) extent of the screen. Thus, for *looming trials*, centered images occupied 25%, then 50%, then 75% and then 100% of the screen. For *receding trials*, centered images occupied 100%, then 75%, then 50% and then 25% of the screen (see Fig. 1). Following these presentations was a 1250 ms fixation. Participants simply had to respond via button press as soon as they perceived the image. The button press had no impact on task presentation. In short, the task had minimal task demands. The task is designed to identify neural regions responding to the stimulus parameters, but to not activate regions involved in response selection and control. Each image was presented once looming and once receding. The task involved 4 runs each consisting of 80 image trials (10 of each of the 8 trial types).

MRI Parameters and Preprocessing

Participants were scanned using a 3-T GE scanner and were analyzed in Analysis of Functional Neuroimages (AFNI; Cox 1996). Specific parameters have been reported elsewhere (Coker-Appiah et al. 2013) and are available in the Supplemental Materials.

General Linear Model Analysis

The model involved six motion regressors and the following task regressors: (i) looming, threatening, animate; (ii) looming, threatening, inanimate; (iii) looming, neutral, animate; (iv) looming, neutral, inanimate; (v) receding, threatening, animate; (vi) receding, threatening, inanimate; (vii) receding, neutral, animate; (viii) receding, neutral, inanimate. All regressors were created by convolving the train of stimulus events with a gamma variate hemodynamic response function to account for the slow hemodynamic response. The participants' anatomical scans were then individually registered to the Talairach and Tournoux atlas (Talairach and Tournoux 1988) – studies have shown that normalization of brain volumes from age 7–8 years onward does not introduce major age-related distortions in localization or time course of the blood-oxygen-level-dependent (BOLD) signal in event-related fMRI (Burgund et al. 2002; Kang et al. 2003). The individuals' functional EPI data were then registered to their Talairach anatomical scan. Linear regression modeling was performed using the 8 regressors described above plus regressors to model a first-order baseline drift function. This produced a β coefficient and associated *t* statistic for each voxel and regressor.

fMRI Data Analysis

The group analysis of the BOLD data was performed on the regression coefficients from the individual subject analyses. First, BOLD response data from TD youth and youth with DBDs was contrasted using a 2 (diagnosis: DBD, TD) × 2 (direction: looming, receding) × 2 (emotion: threat or neutral) × 2 (animacy: animate, inanimate) repeated-measures

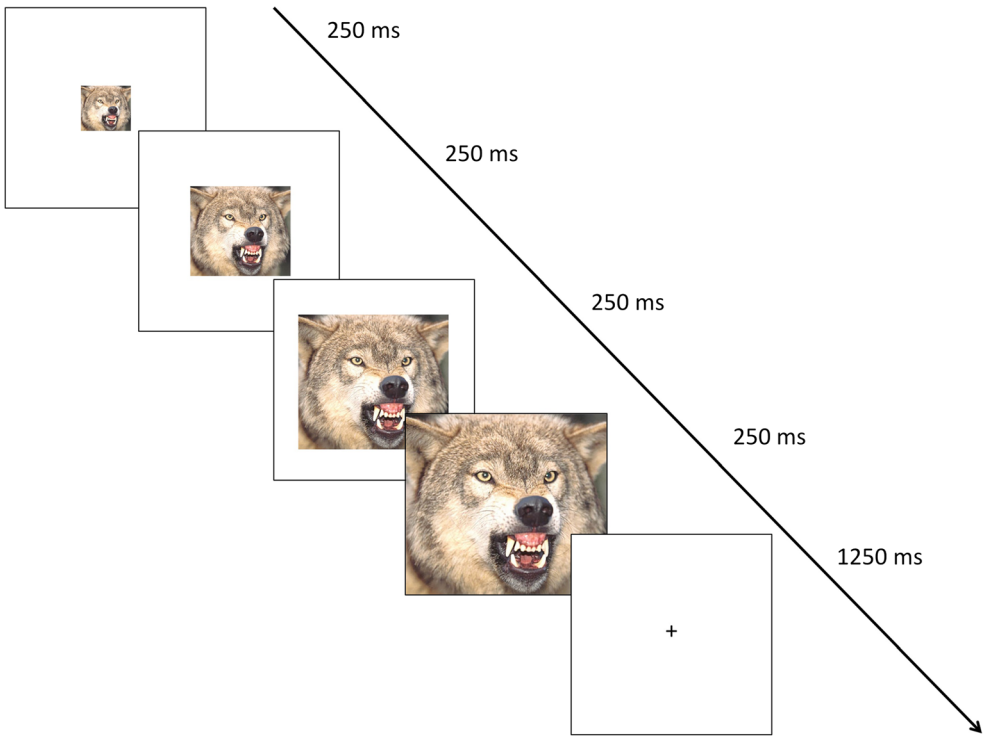

Fig. 1 The Looming Task. Each trial consisted of a serial presentation of images that either increased in visual angle (looming trial, depicted in the figure) or decreased in visual angle (receding trial). Images were looming and animate, looming and inanimate, receding and animate or receding and inanimate. Participants pressed a button as soon as they saw the image

Analysis of Variance (ANOVA). Second, within DBD youth only, a 2 (diagnosis: DBD, TD) × 2 (direction: looming, receding) × 2 (emotion: threat or neutral) × 2 (animacy: animate, inanimate) repeated-measures Analysis of Co-Variance (ANCOVA) was conducted using CU traits as a covariate. Given their small size and theoretical importance, ROI analyses were conducted for the amygdala and PAG ROIs. The amygdala ROIs were drawn from the Eickhoff-Zilles Architectonic Atlas (50% probability; Amunts et al. 2005). The PAG ROI was a 10 mm sphere centered on coordinates (xyz = 3,-23,-4) from Mobbs et al. (2007). The AFNI 3dClustSim program was used to establish a family-wise error correction for multiple comparisons for the ROIs and for the whole brain. This yielded a threshold of 6 voxels for the amygdala and 9 voxels for PAG at an initial threshold of $p = .02$ and a threshold of 18 voxels at an initial threshold of $p = .005$ for the whole brain. Post-hoc analyses of significant main effects and interactions for ROI and whole brain analyses were assessed with planned *t*- tests within SPSS 22.0 (IBM 2012).

Results

Behavioral Results

A 2 (diagnosis: DBD, TD) × 2 (direction: looming, receding) × 2 (emotion: threat or neutral) × 2 (animacy: animate, inanimate) repeated-measures ANOVA was conducted on response latencies. A significant main effect of animacy was observed [$F(1,56) = 4.53$, $p = .04$]; participants responded faster to animate relative to inanimate stimuli. No other significant effects or interactions were observed [F's < 1.31, $p > .26$]. A 2 (direction: looming, receding) × 2 (emotion: threat or neutral) × 2 (animacy: animate, inanimate) repeated-measures ANCOVA was conducted on response latencies of the DBD youth using CU traits as a covariate. No significant effects or interactions were observed [F's < 4.04, $p > .05$].

fMRI Results

Hypothesis 1 Youth with DBDs, relative to TD youth, would show reduced responses to negative relative to neutral images, looming relative to receding stimuli and animate relative to inanimate stimuli within the amygdala, PAG (negative relative to neutral/looming relative to receding only) and connected cortical regions (specifically, temporal, lateral frontal and parietal cortices). This was tested via a 2 (diagnosis: DBD or TD) × 2 (direction: looming, receding) × 2 (emotion: threat or neutral) × 2 (animacy: animate, inanimate) repeated-measures ANOVA on the BOLD response data from within the PAG and bilateral amygdala ROIs and the whole-brain. Predicted findings with respect to our ROI and whole brain results are presented below (see also, Table 1). For additional results, see Supplemental Results.

Regions of Interest

Amygdala: Diagnosis-by-Direction-by-Emotion Interaction TD youth, relative to youth with DBDs, showed, relative to receding neutral stimuli, significantly increased responding in bilateral amygdala during looming threats [right only; $t = 2.63$, $p = .01$], receding threats [$t = 2.13$ & 2.96, $p < .04$] and looming neutral stimuli [$t = 2.53$ & 3.44, $p < .01$] (see Fig. 2A/S1A). The groups did not differ in responsiveness to receding neutral stimuli [$t = 1.55$ & 0.15, $p > .13$].

Diagnosis-by-Emotion Interaction TD youth, relative to youth with DBDs, showed significantly increased responding (albeit k = 5 voxels) during threats relative to neutral trials [right only; $t = 2.66$, $p = .01$].

PAG: Diagnosis-by-Direction-by-Emotion Interaction TD youth, relative to youth with DBDs, showed significantly increased responding during receding threats [$t = 2.06$, $p = .04$], though not during looming threats or looming neutral stimuli [$t = 0.64$ & 1.32, $p > .19$], relative to receding neutral stimuli (see Fig. 2B/S1B). The groups did not differ in responsiveness to receding neutral stimuli [$t = 0.21$, $p = .83$].

Diagnosis-by-Direction Interaction In the diagnosis-by-direction interaction, youth with DBDs showed a greater reduction in PAG response to receding relative to looming stimuli [$t = 2.37$, $p = .021$] compared to TD youth.

No significant interactions between diagnosis and animacy were observed in either region.

Whole-Brain Findings

Diagnosis-by-Direction-by-Emotion Interaction A significant diagnosis-by-direction-by-emotion interaction was observed in regions including left insula cortex, thalamus and right middle temporal/occipital cortex. In insula cortex, TD youth, relative to youth with DBDs, showed a significantly greater increase in BOLD response to looming threats relative to receding threats [$t = 2.76$, $p < .01$], but there were no group differences to looming neutral relative to receding neutral stimuli [$t = 1.96$, $p = .06$]. In middle temporal/occipital cortex and thalamus, TD youth, relative to youth with DBDs, showed significantly greater BOLD responses to receding threats [$t = 3.63$ & 2.34, $p < .03$] and looming neutral stimuli [$t = 2.98$ & 2.16, $p < .04$], though not looming threats [$t = 1.82$ & 0.06, $p > .07$], relative to receding neutral stimuli to which the groups did not differ in responsiveness [$t = 0.64$ & 0.54, $p > .53$].

Table 1 Differential BOLD Response from an Analysis of Variance in Amygdala and Periaqueductal Gray Regions of Interest and Brain Regions Demonstrating Key Significant Effects and Interactions from an Analysis of Variance on BOLD Response during the Looming Task in 31 Youths with DBDs and 27 Typically Developing Youth

			Coordinates of Peak Activation [b]						
Region[a]	Left/Right	BA	x	y	z	*F*	*p*	$\eta^2_{partial}$	Voxels
Region of Interest Results									
Diagnosis-by-Direction-by-Emotion Interaction									
amygdala	Left		−25.5	−1.5	−21.5	10.59	0.0019	0.160	14
amygdala	Right		28.5	1.5	−24.5	13.00	0.0006	0.152	16
periaqueductal gray	Right		1.5	−22.5	−0.5	9.71	0.0028	0.104	15
Diagnosis-by-Emotion Interaction									
amygdala	Right		34.5	−1.5	−18.5	12.24	0.0009	0.148	5
Diagnosis-by-Direction Interaction									
periaqueductal gray	Left		−4.5	−25.5	−0.5	8.73	0.0045	0.091	9
Whole Brain Results									
Diagnosis-by-Direction-by-Emotion Interaction									
insula cortex	Left	13	−40.5	−4.5	5.5	16.17	0.0002	0.188	30
thalamus	Right		16.5	−10.5	5.5	18.01	<0.0001	0.178	18
middle temporal/occipital cortex	Right	19/37	25.5	−64.5	5.5	15.40	0.0002	0.192	176
Diagnosis-by-Emotion-by-Animacy Interaction									
middle frontal gyrus	Left	9	−25.5	43.5	38.5	14.45	0.0003	0.226	58
inferior frontal gyrus	Right	46	31.5	28.5	11.5	14.65	0.0003	0.136	23
inferior parietal cortex	Right	2/40	46.5	−25.5	29.5	13.07	0.0006	0.063	41
lentiform nucleus	Left		−31.5	−10.5	−0.5	17.02	0.0001	0.144	30
middle cingulate gyrus	Right	24	1.5	−13.5	38.5	11.78	0.0011	0.095	33
precentral gyrus	Right	4	28.5	−28.5	47.5	11.00	0.0016	0.091	22
inferior occipital gyrus	Right	18	46.5	−76.5	−0.5	16.97	0.0001	0.186	33
cuneus	Right	17	16.5	−94.5	−0.5	15.66	0.0002	0.256	18
Diagnosis-by-Direction Interaction									
temporal pole/uncus	Right	38	31.5	13.5	−24.5	15.65	0.0002	0.110	21
lentiform nucleus/putamen	Left		−19.5	7.5	−3.5	14.40	0.0035	0.118	21
precentral	Right	4	28.5	−28.5	56.5	12.39	0.0008	0.087	57
precentral	Left	6	−19.5	−16.5	65.5	11.90	0.0010	0.105	26
cuneus	Right	31	19.5	−70.5	17.5	17.79	<0.0001	0.139	137
culmen	Left	19	−13.5	−52.5	−3.5	14.02	0.0004	0.148	48
Diagnosis-by-Emotion Interaction									
superior frontal gyrus	Right	6	10.5	19.5	56.5	13.62	0.0005	0.109	28
anterior insula cortex/inferior frontal gyrus	Left	13/44	−43.5	13.5	17.5	18.45	<0.0001	0.197	18
middle temporal gyrus	Right	22	55.5	−34.5	5.5	12.17	0.0009	0.110	29
supramarginal gyrus	Right	40	58.5	−49.5	29.5	13.41	0.0005	0.091	18
caudate	Left		−13.5	10.5	2.5	15.54	0.0002	0.159	45
caudate	Right		13.5	16.5	2.5	12.58	0.0008	0.119	33
putamen	Right		19.5	−4.5	17.5	14.91	0.0003	0.144	32
precuneus	Left	7	−13.5	−76.5	44.5	22.29	<0.0001	0.213	28
Diagnosis-by-Animacy Interaction									
superior temporal gyrus	Right	13	46.5	−19.5	8.5	13.97	0.0004	0.111	57
supramarginal gyrus	Left	39	−49.5	−58.5	32.5	15.05	0.0003	0.127	26
parahippocampal gyrus	Left	35	−22.5	−25.5	−18.5	16.83	0.0001	0.232	58
Main Effect of Diagnosis									
ventromedial prefrontal cortex	Right	10/32	1.5	40.5	−3.5	19.75	<0.0001	0.220	56

Table 1 (continued)

Coordinates of Peak Activation [b]									
Region[a]	Left/Right	BA	x	y	z	*F*	*p*	$\eta^2_{partial}$	Voxels
dorsomedial frontal cortex	Right	9	1.5	49.5	20.5	18.17	<0.0001	0.187	46
posterior cingulate cortex	Left	31	−13.5	−49.5	35.5	13.57	0.0005	0.220	30
caudate	Right		16.5	22.5	2.5	21.05	<0.0001	0.211	19
temporal pole/uncus	Left	28	−22.5	7.5	−24.5	20.16	<0.0001	0.294	52
superior temporal gyrus	Right	21	58.5	−22.5	2.5	11.64	0.0012	0.100	20
inferior parietal cortex	Left	40	−49.5	−40.5	32.5	15.65	0.0002	0.111	18
precentral gyrus	Right	6	46.5	−7.5	8.5	15.67	0.0002	0.179	63
paracentral lobule	Right	31	4.5	−25.5	44.5	16.88	0.0001	0.284	334
lingual gyrus	Right	18	28.5	−58.5	2.5	12.80	0.0007	0.189	33

[a] According to the Talairach Daemon Atlas (http://www.nitrc.org/projects/tal-daemon/)

[b] Based on the Tournoux & Talairach standard brain template, BA = Brodmann's Area

Diagnosis-by-Direction Interaction A diagnosis-by-direction interaction was observed in regions including right temporal pole/uncus and left lentiform nucleus/putamen. In both regions, TD youth, relative to youth with DBDs, showed a greater difference in BOLD response to looming relative to receding stimuli [$t = 2.63$ & 2.73, $p < .011$].

Diagnosis-by-Emotion Interaction A diagnosis-by-emotion interaction was observed in regions including superior frontal gyrus, left aIC/iFG, right middle temporal, right supramarginal gyrus, bilateral caudate and right putamen. In all regions, TD youth, relative to youth with DBDs, showed a greater increase in BOLD response to threat relative to neutral stimuli [$t = 2.37$ to 3.71, $p < .021$].

Diagnosis-by-Emotion-by-Animacy Interaction A significant diagnosis-by-emotion-by-animacy interaction was observed in regions including left middle frontal gyrus, right iFG and right inferior parietal cortex. In all regions, TD youth showed a significantly greater increase in BOLD response to

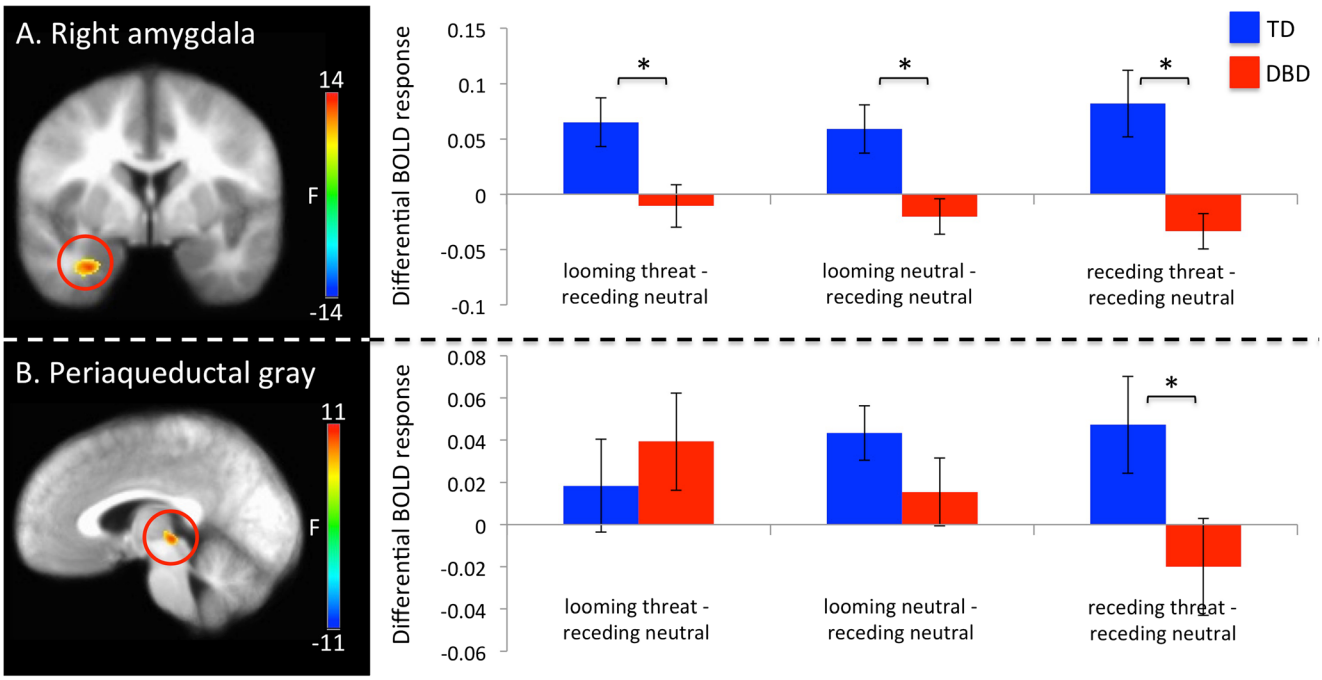

Fig. 2 Regions of Interest Showing a Significant Diagnosis-by-Direction-by-Emotion Interaction. **A** Significant activations within the right amygdala region of interest where increased BOLD responses to [looming threat – receding neutral], [looming neutral –receding neutral] and [receding threat – receding neutral] were observed in typically developing youth (TD; $N = 27$) compared to youth with disruptive behavior disorders (DBDs; $N = 31$); **B** Significant activations within the periaqueductal gray region of interest where increased BOLD responses to [receding threat – receding neutral] were observed in TD youth compared to youth with DBDs

threat relative to neutral animate stimuli [t = 2.44 to 3.44, p < .02], but not threat relative to neutral inanimate stimuli [t = .42 to 1.87, p > .07] relative to youth with DBDs.

Diagnosis-by-Animacy Interaction A diagnosis-by-animacy interaction was observed in regions including left fusiform/parahippocampal gyrus, left inferior parietal/supramarginal gyrus and right postcentral/superior temporal gyrus. In fusiform/parahippocampal gyrus and inferior parietal/supramarginal gyrus, TD youth, relative to youth with DBDs, showed a significantly greater increase in BOLD response to animate relative to inanimate stimuli [t = 4.11 & 2.86, p < .01]. In right postcentral/superior temporal gyrus gyrus, TD youth, relative to youth with DBDs, showed a significantly greater decrease in BOLD response to animate relative to inanimate stimuli [t = 2.64, p = .01].

Hypothesis 2 Within the youth with DBDs, CU traits would be inversely associated with responsiveness to looming, negative and animate stimuli within the amygdala, PAG (negative relative to neutral/looming relative to receding only) and connected cortical regions (specifically, temporal, lateral frontal and parietal cortices). This was tested via a 2 (direction: looming, receding) × 2 (emotion: threat or neutral) × 2 (animacy: animate, inanimate) repeated-measures ANCOVA on the BOLD response data from only the youth with DBDs using CU traits as a covariate (see Table 2).

Regions of Interest

No significant key interactions were identified within these regions.

Whole-Brain Findings

CU Traits-by-Direction-by-Emotion A significant CU traits-by-direction-by-emotion interaction was observed in regions including medial superior frontal cortex and right superior frontal cortex. In both regions, CU traits were more inversely related to BOLD responses to receding threats [Steiger's Z = 2.18 & 2.36, p < .03] and looming neutral stimuli [Steiger's Z = 2.50 & 2.26, p < .03] than receding neutral stimuli. No difference in the magnitude of relationship between CU traits and BOLD response was observed to looming threats relative to receding neutral stimuli [Steiger's Z = 0.07 & 0.93, p > .35].

CU Traits-by-Direction A significant CU traits-by-direction interaction was observed in regions including left middle frontal cortex, left iFG, left STG and two regions of left inferior parietal cortex (see Fig. 3). In all regions, CU traits were more inversely related to BOLD responses in looming trials [r = −.05 to −.44] relative to receding trails [r = −.02 to .28; Steiger's Z = 2.19 to 2.68, p < .02].

CU Traits-by-Animacy A significant CU traits-by-animacy interaction was observed in regions including PCC and left lingual gyrus. In both regions, a stronger negative association between CU traits and animate stimuli [r = −.39 & -.45] relative to inanimate stimuli [r = .08 & -.2, Steiger's Z = 2.40 & 2.04, p < .04] was observed.

Potential Confounds

As over half of the youth with DBDs were either taking a medication that could not be withheld during scanning or met criteria for attention-deficit/hyperactivity disorder (ADHD), the ANOVA was re-conducted removing these youth from the analysis. When removing youth taking medications, the effects of interest were replicated with proximal activations in the same brain regions for all contrasts except in supramarginal gyrus in the diagnosis-by-emotion interaction. Some regions were significant, however, only at more lenient thresholds (see Supplemental Materials/Table S3). When removing youth with ADHD, the effects of interest were replicated with proximal activations in the same brain regions for all contrasts except in supramarginal gyrus in the diagnosis-by-emotion interaction. Some regions were significant, however, only at more lenient thresholds (see Supplemental Materials/Tables S4).

Discussion

The goal of the current study was to examine responsiveness to core threat variables (visual threats and encroaching stimuli) and animacy information in youth with DBDs and to determine the extent to which this responsiveness varies with level of CU traits. There were three main findings: First, evidence of reduced responsiveness to threat variables, including both visual threats and encroaching stimuli, was observed within both acute threat circuitry (amygdala and PAG) and temporal, lateral frontal and parietal cortices in youth with DBDs. Second, youth with DBDs also showed reduced responsiveness to animacy information within temporal, lateral frontal and parietal cortices, but not acute threat circuitry. Third, within the youth with DBDs increasing CU traits were associated with decreased responsiveness in cortical regions to both core threat variables and animacy information.

Our first hypothesis was that youth with DBDs, relative to TD youth, would show reduced responses to negative relative to neutral images, looming relative to receding stimuli and animate relative to inanimate stimuli within the amygdala, PAG (negative relative to neutral/looming

Table 2 Brain Regions Demonstrating Key Significant Effects and Interactions from an Analysis of Covariance on BOLD Response during the Looming Task Utilizing Callous-Unemotional Traits as a Covariate in 31 Youths with DBDs

Coordinates of Peak Activation [b]									
Region[a]	Left/Right	BA	x	y	z	*F*	*p*	$\eta^2_{partial}$	Voxels
Callous-Unemotional Traits-by-Direction-by-Emotion Interaction									
superior frontal cortex	Right	9	1.5	55.5	32.5	17.91	0.0002	0.349	29
superior frontal cortex	Right	9	34.5	46.5	29.5	20.67	<0.0001	0.442	20
Callous-Unemotional Traits-by-Direction Interaction									
middle frontal cortex	Left	9	−34.5	7.5	38.5	18.67	0.0002	0.162	32
inferior frontal gyrus	Left	44/13	−46.5	4.5	2.5	14.82	0.0006	0.206	28
superior temporal gyrus	Left	21	−61.5	−37.5	−3.5	18.04	0.0002	0.230	27
inferior parietal cortex	Left	7	−31.5	−46.5	56.5	13.95	0.0008	0.249	39
inferior parietal cortex	Left	40	−40.5	−46.5	44.5	14.92	0.0006	0.450	19
precuneus	Left	7	−25.5	−67.5	32.5	14.71	0.0006	0.191	21
cuneus	Right	18	7.5	−82.5	17.5	16.70	0.0003	0.216	33
lingual gyrus	Left	18	−16.5	−82.5	−12.5	14.01	0.0008	0.227	46
Callous-Unemotional Traits-by-Animacy Interaction									
posterior cingulate cortex	Left	29	−1.5	−40.5	8.5	16.34	0.0004	0.238	27
lingual gyrus	Left	18	−7.5	−79.5	−15.5	20.49	<0.0001	0.235	43
precentral gyrus	Left	4	−58.5	−19.5	38.5	18.81	0.0002	0.232	38
middle temporal gyrus	Right	37	55.5	−55.5	2.5	17.28	0.0003	0.263	33
precentral gyrus	Left	9	−43.5	4.5	35.5	14.60	0.0007	0.350	22
culmen	Right		4.5	−58.5	−3.5	21.18	<0.0001	0.363	34

[a] According to the Talairach Daemon Atlas (http://www.nitrc.org/projects/tal-daemon/)

[b] Based on the Tournoux & Talairach standard brain template, BA = Brodmann's Area

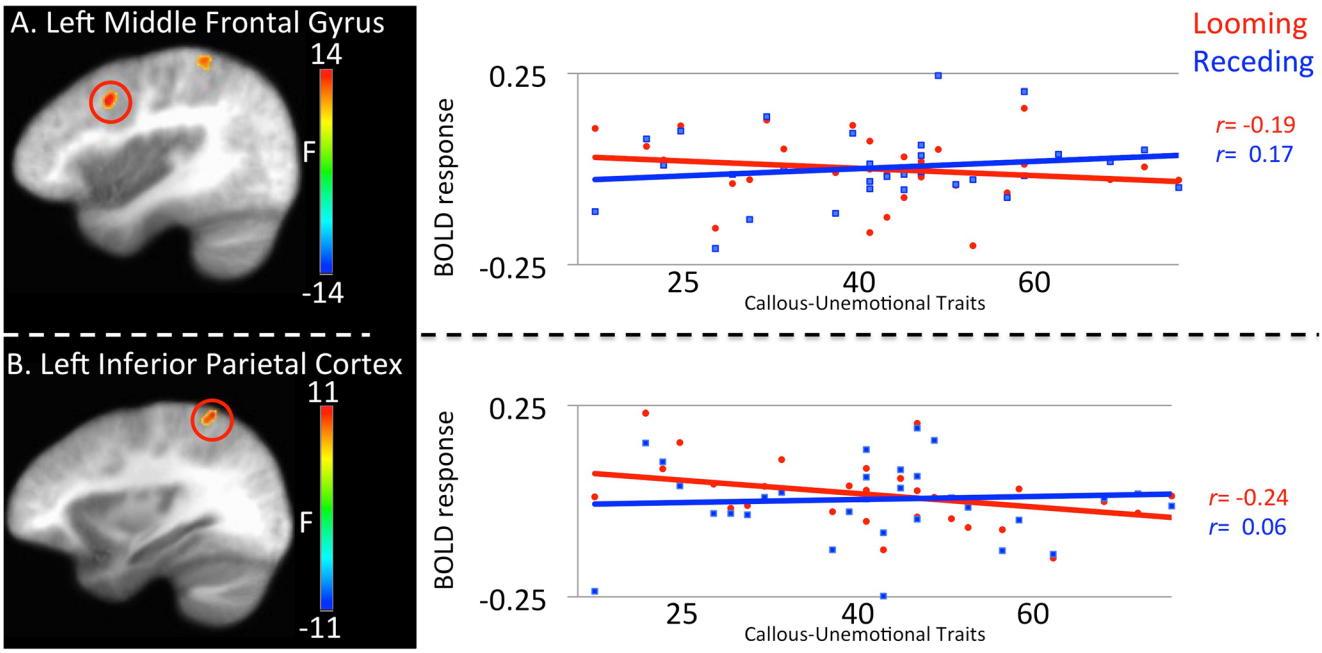

Fig. 3 Regions Showing a Significant Callous-Unemotional Traits-by-Emotion Interaction within the 31 youth with disruptive behavior disorders. In left middle frontal gyrus (**A**) and left inferior parietal cortex (**B**), CU traits showed a significantly larger inverse association with BOLD responses in looming trials relative to receding trails

relative to receding only) and connected cortical regions (specifically, temporal, lateral frontal and parietal cortices). With respect to negative relative to neutral images, this hypothesis was largely confirmed. Youth with DBDs showed reduced responses, relative to TD youth, to negative relative to neutral images within the amygdala and right middle temporal, lateral frontal, left aIC/iFG and right supramarginal gyrus. In short, youth with DBDs showed a reduced response to visual threats both with core emotion circuitry (amygdala; cf. LeDoux 2012), regions highly interconnected with the amygdala implicated in stimulus representation (middle temporal cortex; Caramazza and Shelton 1998; Martin 2007) and regions implicated in attention (supramarginal/parietal cortex; Behrmann et al. 2004; lateral frontal; Bishop et al. 2004; aIC/iFG; Peters et al. 2016). With respect to looming relative to receding stimuli, our hypothesis was somewhat supported. In contrast to predictions, only within the amygdala was the condition hypothesized to be most associated with group differences (looming threats) associated with greater responses in TD youth relative to youth with DBDs. Indeed, within PAG and middle temporal/occipital cortex, group differences were only seen in response to receding threat or looming neutral stimuli (middle temporal/occipital cortex only). In addition, youth with DBDs, relative to TD youth, showed reduced responses to looming stimuli generally within right temporal pole.

There has been relatively little *fMRI* work examining responsiveness to non-social threat stimuli in youth with DBDs. The preponderance of previous fMRI work has considered distress cues, as opposed to threat responsiveness, in youth with DBDs and reported reduced amygdala (and to a lesser extent connected cortical region) responsiveness to fearful expressions (Jones et al. 2009; Lozier et al. 2014; Marsh et al. 2008; Passamonti et al. 2010; Viding et al. 2012; White et al. 2012a). However, there have been reports of reduced amygdala responses to threat stimuli in youth with DBDs (Stadler et al. 2007), particularly for those with low anxiety [Sterzer et al. 2005; see also Hwang et al. 2016 and, for a non-replication, Herpertz et al. 2008]. In line with this earlier work, youth with DBDs in the current study showed reduced responsiveness within amygdala and associated cortical regions to visual threats. They also showed reduced responsiveness within to receding threats and looming neutral stimuli within amygdala, PAG and temporal cortical regions. Reduced threat responsiveness may contribute to risk taking and impulsivity; the individual may be more likely to engage in risky behaviors, as they are less afraid of the consequences. However, it is possible that reduced threat responsiveness contributes little to the behavioral profile of youth with behavioral problems. The systems engaged by threat stimuli are also those engaged by distress cues (particularly the amygdala; Blair 1995, 2007, 2013). As such, reduced threat responsiveness may simply reflect dysfunction in the neural systems that respond to distress cues, as these systems also process threat.

With respect to animate relative to inanimate stimuli, our first hypothesis was partly supported. Youth with DBDs showed reduced responses to animate relative to inanimate stimuli in fusiform gyrus and inferior parietal gyrus. In addition, youth with DBDs showed reduced responses to animate relative to inanimate stimuli within left middle frontal gyrus, right iFG and right inferior parietal cortex, to threatening, and not neutral, animate stimuli. It should be noted that all these regions have been shown to be responsive to animacy information, including point light and shape animation displays of biological motion (Bi et al. 2016; Lu et al. 2016; Osaka et al. 2012; Shultz and McCarthy 2014; Shultz et al. 2015). The amygdala is also highly sensitive to animacy information (Beauchamp et al. 2003; Cao et al. 2014; Coker-Appiah et al. 2013; Wheatley et al. 2007). Indeed, there have been suggestions that during social cognition, the amygdala signals the presence of socially relevant information to these other regions involved in social cognition (Ochsner 2008). As such, it remains unclear whether i) youth with DBDs show intact amygdala response to animacy information, but either fail to propagate this information to cortical regions or these cortical regions themselves are dysfunctional or ii) the failure to observe amygdala dysfunction in the current study is the result of type II error. Future work will need to differentiate between these hypotheses.

Our second hypothesis was that, within the youth with DBDs, CU traits would be inversely associated with responsiveness to looming, negative and animate stimuli within the amygdala, PAG (negative relative to neutral/looming relative to receding only) and connected cortical regions (specifically, temporal, lateral frontal and parietal cortices). With respect to responsiveness to looming stimuli, our second hypothesis was partly confirmed. Indeed, the moderating effects of CU traits within the youth with DBDs partly echoed the differences between youth with DBDs and typically developing youth. CU traits were more inversely related to BOLD responses to receding threat or looming neutral stimuli rather than looming threats within medial and lateral superior frontal cortex. Moreover, increased CU traits were associated with relatively suppressed responding to looming stimuli in a series of regions (left middle frontal cortex, left iFG, left STG and two regions of left inferior parietal cortex). As such, our data appear to offer some support for the suggestion that within the youth with DBDs, CU traits are inversely associated with responsiveness to threat stimuli (cf. Hwang et al. 2016). However, this support is driven by findings relating to the looming manipulation. In this study, CU traits had no significant impact on responsiveness to visual threats. Moreover, CU traits were only inversely associated with responsiveness to threat stimuli in cortical regions, not the amygdala. Previous work has reported reduced responsiveness to visual threat

stimuli as a function of level of CU traits within vmPFC in youth with DBDs (Hwang et al. 2016). However, that result was not replicated here (albeit in a very different paradigm).

With respect to responsiveness to animate stimuli, our second hypothesis was not confirmed. Levels of CU traits were not related to responsiveness within the amygdala or temporal, lateral frontal and parietal cortices to animacy information in this study. However, they were related to animacy responsiveness within PCC and a proximal region of lingual gyrus. PCC is critically implicated in social cognition. However, it has been attributed a role in high-level mental state inference (Ochsner 2008). The current task did not incorporate any element of high-level mental state inference. It is possible that the dysfunction seen in the current study relates to one of the other functions that PCC is implicated in, such as providing the functional linkage of motivational and oculomotor information (McCoy and Platt 2005). Alternatively, PCC may have a role in lower level social cognition processing that is not yet well defined. Future work will need to examine these possibilities, as well as examine whether the PCC dysfunction observed here accounts for the asociality observed in youth with high levels of CU traits.

The current data need to be interpreted in light of six caveats. First, the current study did not include an ADHD-only comparison group, nor were symptom levels available for examination. However, this caveat is mitigated by a secondary analysis, which excluded youth with ADHD and revealed fundamentally similar results (see Supplemental Materials). Second, five youth with DBDs were taking medication that could not be withheld during scanning. Again, this caveat is mitigated by a secondary analysis excluding these youth, which did not reveal fundamentally different results (see Supplemental Materials). Third, while adequately powered to detect the hypothesized group differences, the current study was possibly under-powered to detect differences across all contrasts reported. Replication in larger samples will be important. Fourth, the sample encompassed a relatively broad developmental range. Future work closely examining both age and pubertal development will be needed to more accurately interpret the current data. Fifth, the current study was under-powered to investigate the role of gender, despite there being some evidence of gender differences in the neural underpinnings of DBDs (Baker et al. 2015). Future work will need to focus on this issue. Sixth, the current sample had relatively fewer comorbid psychiatric disorders than would be expected in a typical clinic. Strict inclusion criteria allow for increased specificity regarding which symptom sets might be underpinned by the neural dysfunction observed in the current study. However, this approach limits the generalizability of the findings.

In summary, the current study found evidence of reduced responsiveness to threat variables, including both visual threats and encroaching stimuli, within both acute threat circuitry (amygdala and PAG) and temporal, lateral frontal and parietal cortices in youth with DBDs. This reduced responsiveness, at least with respect to the looming variable, was modulated by CU traits. Reduced threat responsiveness may contribute to risk taking and impulsivity in youth with DBDs, particularly those with high levels of CU traits. Second, youth with DBDs also showed reduced responsiveness to animacy information within temporal, lateral frontal and parietal cortices, but not within amygdala. Within the youth with DBD, reduced responsiveness to animacy information was observed in PCC as a function of CU trait level. Future work will need to examine responsiveness to animacy information in youth with DBD, the potential role of PCC and the extent to which any dysfunction might relate to the social difficulties shown by many of these youth.

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Compliance with Ethical Standards

Conflict of Interest No authors have any conflicts of interest to disclose.

Ethical Approval This study was approved by the National Institutes of Health Combined Neurosciences Institutional Review Board (protocol number 05-M-0105). All research procedures were compliant with relevant U.S. and National Institutes of Health ethics policies and regulations.

Informed Consent Written informed consent was obtained from the legal guardians of all participants and written assent was obtained from all participants.

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