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The processing of animacy information is disrupted as a function of callous-unemotional traits in youth with disruptive behavior disorders

Laura C. Thornton[a,*], Elizabeth A. Penner[b], Zachary T. Nolan[c], Christopher J. Adalio[d], Stephen Sinclair[e], Harma Meffert[a], Soonjo Hwang[b], R. James R. Blair[a,e], Stuart F. White[a]

[a] Center for Neurobehavioral Research, Boys Town National Research Hospital, Boys Town, NE, United States
[b] Univeristy of Nebraska Medical Center, Omaha, NE, United States
[c] Pennsylvania State University School of Medicine, Hershey, PA, United States
[d] Univeristy of California, Berkeley, Berkeley, CA, United States
[e] National Institute of Mental Health, NIH, Bethesda, MD, United States

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ABSTRACT

Atypical amygdala responses to emotional stimuli have been consistently reported in youth with Disruptive Behavior Disorders (DBDs; Conduct Disorder/Oppositional Defiant Disorder). However, responding to animacy stimuli has not been systematically investigated. Yet, the amygdala is known to be responsive to animacy stimuli and impairment in responsiveness to animacy information may have implications for social cognitive development. Twenty-nine youth with DBDs and 20 typically developing youth, matched for IQ, age (M_{age} = 14.45, SD = 2.05) and gender, completed a dot probe task during fMRI. Stimuli consisted of negative/faces, negative/objects, neutral/faces and neutral/objects images. Youth with DBDs, relative to typically developing youth, showed: i) reduced amygdala and lateral temporal cortex responses to faces relative to objects. Moreover, within the group of youth with DBDs, increasing callous-unemotional traits were associated with lesser amygdala responses to faces relative to objects. These data suggest that youth with DBDs, particularly those with high levels of CU traits exhibit dysfunction in animacy processing in the amygdala. This dysfunction may underpin the asociality reported in these youth.

1. Introduction

Disruptive Behavior Disorders (DBDs), which include Conduct Disorder and Oppositional Defiant Disorder, are a leading cause of referrals to mental health practitioners for children and adolescents (Kazdin et al., 2006). Youth with DBDs are at increased risk for aggression and antisocial behavior (Frick et al., 2005). Furthermore, prognosis is poor, with many of these youth showing significant aggression in adulthood (Fergusson et al., 2010; Robins, 1966). Recent neuroimaging work has implicated amygdala dysfunction in the pathology of DBDs (Blair et al., 2014). However, the functional characteristics of this amygdala dysfunction remain under-studied.

The amygdala engages in emotional processing (LeDoux, 2012) showing greater responses to threat and appetitive stimuli relative to neutral stimuli (Zald, 2003), stimuli previously associated with aversive reinforcers relative to stimuli not associated with such reinforcers (Pape and Pare, 2010) and fearful expressions relative to neutral expressions (Murphy et al., 2003). The amygdala is thought to prime representations of emotional stimuli within temporal cortex, through reciprocal interactions with this region (Desimone and Duncan, 1995; Pessoa and Ungerleider, 2004; Vuilleumier, 2005). The amygdala is also sensitive to animacy information. The amygdala shows greater responses to animate stimuli, particularly faces (Gobbini et al., 2011; Yang et al., 2012), but also animals (Coker-Appiah et al., 2013; Yang et al., 2012), and inanimate objects moving in animate ways (Martin and Weisberg, 2003; Wheatley et al., 2007) relative to inanimate stimuli. Lateral regions of temporal cortex, including lateral fusiform gyrus and posterior superior temporal sulcus, show increased response to animate relative to inanimate stimuli (Martin, 2007). It is assumed that the amygdala similarly primes cortical representations of animate stimuli within these regions, similar to representations of emotional stimuli (Dunsmoor et al., 2014).

Youth with DBDs show disrupted amygdala responses to emotional stimuli (Crowe and Blair, 2008; Marsh and Blair, 2008) together with reduced lateral temporal cortex responses (for meta-analysis see Alegria et al., 2016), presumably due to reduced priming by the amygdala. The severity of amygdala disruption is positively associated with the level of a particular symptom set; callous-unemotional (CU) traits (lack of guilt/

* Corresponding author at: 14100 Crawford St., Boys Town, NE 68010, United States.
E-mail address: laura.thornton@boystown.org (L.C. Thornton).

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empathy, deficient affect; Viding et al., 2012; White et al., 2012a). CU traits represent an important subgroup of antisocial youth (Frick et al., 2014) and are captured by the "with Limited Prosocial Emotions" specifier for Conduct Disorder in the Diagnostic and Statistical Manual of Mental Disorders – 5th Edition (American Psychiatric Association, 2013).

Notably though, the functional integrity of other roles of the amygdala, for example responsiveness to animacy, in youth with DBDs and their relationship with CU trait severity remains unknown. One prototypical animate stimulus, known to activate the amygdala, is the human face (Gobbini et al., 2011; Yang et al., 2012). Considerable previous work has examined responsiveness to face stimuli in youth with conduct problems and CU traits (see Marsh and Blair, 2008 for meta-analysis). However, the majority of these studies have examined the contrast between responsiveness to emotional relative to neutral face stimuli (Jones et al., 2009; Marsh et al., 2008; Viding et al., 2012; White et al., 2012a). In other words, work has not typically specifically examined group differences in responsiveness to *neutral* face stimuli. Responsiveness to neutral stimuli has been treated as a high-level baseline stimulus, which allows for contrasting the responsiveness to emotional face stimuli. One exception to this, Marsh et al. (2008) did suggest intact responding to neutral faces in a sample of youth with DBD and psychopathic traits. However, our preliminary recent re-analysis of neutral face data from White et al. (2012a) revealed reduced responsiveness in youth with DBD and elevated CU traits to neutral faces. As such, we considered it useful to examine responsiveness to this form of animate stimuli in a targeted study of youth with DBD.

Determining the functional integrity of the amygdala during animacy processing in youth with DBDs, particularly as a function of CU traits, is important for two reasons. First, response to animacy information is considered critical for social engagement (Wheatley et al., 2007), particularly within the amygdala (Ochsner, 2008). As such, dysfunctional animacy processing might contribute to the social disengagement associated with CU traits (e.g., attachment problems; Bohlin et al., 2012; Pasalich et al., 2012) and/or the disruption of socialization reported in youth with CU traits (Frick et al., 2014; Frick and White, 2008). Second, response to animacy information has implications for future interventions. As interventions become targeted for specific neuro-cognitive impairments, it is important to know whether the clinician's target should be modifying the individual's amygdala responsiveness to emotional stimuli selectively or generally increase amygdala responsiveness.

The current study utilized a dot probe paradigm (MacLeod et al., 1986). Such a paradigm allows assessment of both behavioral responses and neural responsiveness to both neutral and emotional animate stimuli. More critically, it allows assessment of responsiveness to these variables "passively"; without task demands that focus on the core variables. That is, to respond to the dot probe, not the animacy/emotional components of the visual stimuli. As such, this paradigm shared similarities with our previous work that has examined amygdala responsiveness to distress cues in this population (task demands in this work focus on the person's gender rather than their affect; e.g., Mitchell et al., 2007; White et al., 2012a). In addition, such a paradigm allows assessment of the participant's capacity for response inhibition via their differential responsiveness to the congruence/incongruence of the visual location of the visual stimulus and the probe. Notably, an association between dysfunctional response inhibition and externalizing behaviors (Patrick et al., 2013; Young et al., 2009), particularly impulsivity (Krueger et al., 2007; Loeber et al., 2009), has been made for some time. Moreover, recent work has indicated that youth with DBDs show reduced responsiveness in systems mediating response inhibition (although this impairment relates to impulsiveness rather than CU traits; Hwang et al., 2016).

The current study tests two hypotheses. First, youth with DBDs, relative to TD youth, would show reduced responses to negative relative to neutral images and animate relative to inanimate stimuli within the amygdala and lateral temporal cortex. Second, within the youth with DBD, CU traits would be inversely associated with responsiveness to negative and animate stimuli within the amygdala and lateral temporal cortex.

2. Methods

2.1. Participants

Fifty-two youth participated, though the final sample was 49 youth: 29 youth with DBDs and 20 typically developing (TD) youth aged 10–17 years. Three youth (1 TD youth and 2 youth with DBDs) were excluded for excessive movement (see MRI parameters and data preprocessing). 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 youth and parents. The NIH Combined Neurosciences Institutional Review Board approved this study. All youth and parents completed the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS; 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). The K-SADS assesses for substance abuse and substance dependence but, due to exclusion criteria, no children in either group met criteria for these diagnoses. IQ was assessed with the Wechsler Abbreviated Scale of Intelligence (two-subtest form; Wechsler, 1999). Exclusion criteria were pervasive developmental disorder, Tourette's syndrome, lifetime history of psychosis, depression, bipolar disorder, generalized, social or separation anxiety disorder, post-traumatic stress disorder, neurologic disorder, history of head trauma, history of substance abuse, 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 DBDs group, while comparison subjects did not meet criteria for any K-SAD diagnosis. The groups did not differ significantly on IQ ($t = 1.511$, $p = 0.138$), age ($t = -1.134$, $p = 0.263$), or gender ($\chi^2 = 1.793$, $p = 0.181$).

2.2. Study measures

2.2.1. Inventory of Callous-Unemotional Traits (ICU; Frick, 2004)

The ICU is a 24-item parent-report scale designed to assess CU traits in youth. The construct validity of the ICU has been supported in community and juvenile justice samples (Essau et al., 2006; Kimonis et al., 2008).

2.2.2. The Animacy Attention Task

The current study used a version of a dot probe task (White et al., 2014). The stimuli consisted of images that were negative and animate (i.e., fearful faces), negative and inanimate (e.g., gun, knife), neutral and animate (i.e., neutral faces), or neutral and inanimate (e.g., mug, hairdryer). Importantly, stimuli were matched such that facial expression stimuli did not differ from the object stimuli on valence, arousal, or luminance (White et al., 2014). Each trial began with a 30 ms fixation, followed by a 300 ms stimulus presentation on either the left of the right side of the screen occupying 40% of the width and 45% of the height of the screen. The stimuli were immediately followed by the presentation of a probe (*) for 1000 ms. During congruent trials the probe appeared on the same side of the screen as the stimulus. During incongruent trials, the probe appeared on the opposite side of the screen to the stimulus. Following the probe was a 970 ms fixation. Participants were asked to make a button press corresponding to the side of the screen the probe appeared on as quickly as possible after the presentation of the probe. The task included 4 runs of 2 m and 10 s each, each consisting of 10 negative faces, 10 negative objects, 10

neutral faces and 10 neutral objects images as well as 10 fixation trials (2300 ms duration), for a total of 40 images per condition. Sixty percent of trials were congruent and images were randomized across trials and participants. All participants not excluded due to movement met the inclusion criteria of having at least 25 correct trials of each image type (i.e., at least 100 correct out of 160 trials).

2.3. MRI parameters and data preprocessing

Participants were scanned using a 3.0 GE Signa scanner and data were analyzed using Analysis of Functional Neuroimages (AFNI; Cox, 1996). A total of 45 functional images per run were taken with a gradient echo planar imaging (EPI) sequence (repetition time = 2900 ms; echo time = 27 ms; 64 × 64 matrix; 90° flip angle; 220 mm field of view). Whole-brain coverage was obtained with 44 contiguous axial slices (thickness, 2.5 mm; 0.5 mm spacing, in-plane resolution, 3.48 × 3.48 mm). A high-resolution anatomical scan (3-dimensional spoiled gradient recalled acquisition in a steady state; repetition time = 7.776 ms; echo time = 2.984 ms; 240 mm field of view; 12° flip angle; 128 axial slices; thickness, 1.2 mm; 256 × 192 matrix) in register with the EPI data set was obtained covering the whole brain (Coker-Appiah et al., 2013).

At the individual level, functional images from the first five repetitions, collected before equilibrium magnetization was reached, were discarded. Functional images from the four time series were despiked, slice-time corrected, motion corrected. TRs that deviated > 0.5 mm in any plane from the previous TR were censored in AFNI. Three youth were excluded as they had > 25% of TRs censored. Visual inspection of the individual participants' data revealed no additional motion artifacts. No significant differences between TD youth and youth with DBDs in the number of censored TRs ($t = 1.43$, $p = 0.16$) or in the maximum displacement over a run ($t = 1.52$, $p = 0.14$). 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 seven to eight 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). After this, the individuals' functional EPI data were then registered to their Talairach anatomical scan, spatially smoothed with a 6 mm full-width half-maximum Gaussian filter, and normalized by dividing the signal intensity of a voxel at each point by the mean signal intensity of that voxel for each run and multiplying the result by 100. Resultant regression coefficients therefore represented a percentage of signal change from the mean.

2.4. fMRI data analysis

Following preprocessing, eight regressors were generated and included in the model: (i) negative faces, congruent; (ii) negative faces, incongruent; (iii) negative objects, congruent; (iv) negative objects, incongruent; (v) neutral faces, congruent; (vi) neutral faces, incongruent; (vii) neutral objects, congruent; (viii) neutral objects, incongruent. There was also a regressor for incorrect trials. 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. Linear regression modeling was performed using the nine 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.

The group analysis of the BOLD data was then performed on the regression coefficients from individual subject analyses. Given our a priori hypotheses of the involvement of the amygdala, regions of interest (ROIs) were obtained for left and right amygdala using an anatomically defined mask (Eickhoff-Zilles Architectonic Atlas: 50% probability mask; Amunts et al., 2005). First, BOLD responses within both the left and right amygdala ROIs and the whole brain were examined with a 2 (diagnosis: DBD, TD) by 2 (animacy: faces, objects) by 2 (congruence: congruent, incongruent) by 2 (emotion: negative, neutral) repeated-measures Analysis of Variance (ANOVA). Second, BOLD responses within both ROIs and the whole brain were examined with a 2 (animacy: faces, objects) by 2 (congruence: congruent, incongruent) by 2 (emotion: negative, neutral) repeated-measures Analysis of Co-Variance (ANCOVA) with level of CU traits as the covariate within the participants with DBD only.

The AFNI 3dClustSim program, using the autocorrelation function (-acf), was used to establish a family-wise error correction for multiple comparisons for the ROIs and for the whole brain (Cox et al., 2017). Using an initial threshold of $p = 0.001$, this yielded an extent threshold of 3 voxels for the amygdala ROIs and 17 voxels for the whole brain. Post-hoc analyses were conducted on the percent signal change taken from all significant voxels within each ROI (left and right amygdala separately) and whole brain functional masks generated by AFNI to examine significant main effects and interactions with planned t-tests within SPSS 22.0 (IBM, 2012).

3. Results

3.1. Behavioral results

Table 1 presents demographic information and zero-order correlations among study variables. Age, IQ, and gender were not associated with task performance or CU traits. Two 2 (diagnosis: DBD, TD) by 2 (emotion: negative, neutral) by 2 (animacy: faces, objects) by 2 (congruence: congruent, incongruent) repeated-measures ANOVAs were conducted on the accuracy and reaction time data. The only significant main effects found were for congruence: such that lower accuracy [$F(1,47) = 11.957$, $p = 0.001$] was found for incongruent ($M = 0.919$) relative to congruent ($M = 0.959$) trials; and reactions [$F(1,47) = 47.178$, $p < 0.001$] were slower for incongruent ($M = 428.323$) relative to congruent ($M = 399.602$) trials.

Two 2 (emotion: negative, neutral) by 2 (animacy: faces, objects) by 2 (congruence: congruent, incongruent) repeated-measures ANCOVAs using CU traits as a covariate were conducted on the accuracy and

Table 1
Descriptive statistics and zero-order correlations among demographic and behavioral variables.

	TD $n = 20$	DBD $n = 29$	t	p	1	2	3	4	5	6
1. Age	14.05	14.72	−1.134	0.263	–					
2. IQ	103.89	99.28	1.511	0.138	−0.126	–				
3. Gender	0.50	0.69	−1.336	0.188	0.114	−0.026	–			
4. CU traits	–	42.59	–	–	−0.268	−0.263	−0.229	–		
5. Reaction time	392.59	435.33	**−2.468**	**0.017**	0.002	0.055	−0.054	**−0.518****	–	
6. Accuracy	0.95	0.93	0.745	0.460	0.041	0.193	−0.061	**0.401***	−0.230	–

Note: Gender was coded 0 = Female, 1 = Male; CU = Callous-Unemotional; CU traits was not collected for TD youth. Significant differences at $p < 0.05$ are bold. *$p < 0.05$, **$p < 0.01$.

reaction time data of the youth with DBDs. These revealed a main effect of animacy for accuracy [$F(1,27) = 12.294$, $p = 0.002$], such that accuracy was poorer for inanimate ($M = 0.921$) relative to animate ($M = 0.937$) stimuli. In addition, interestingly, there was also an *animacy-by-CU traits* interaction for the accuracy data [$F(1,27) = 9.681$, $p = 0.004$]. A larger, positive correlation between CU traits and accuracy was observed for inanimate ($r = 0.461$) relative to animate ($r = 0.304$) stimuli [*Steiger's* $Z = -2.062$, $p = 0.039$]. No significant main effects or interactions were revealed by the reaction time ANCOVA.

3.2. fMRI results

Hypothesis 1. Youth with DBDs, relative to TD youth, would show reduced responses to negative relative to neutral images and animate relative to inanimate stimuli within the amygdala and lateral temporal cortex.

This was examined via a 2 (diagnosis: DBD, TD) by 2 (animacy: faces, objects) by 2 (congruence: congruent, incongruent) by 2 (emotion: negative, neutral) repeated-measures ANOVA conducted on the BOLD response data from within the left and right amygdala ROIs and the whole brain. ROI and whole brain results are presented below (see also, Tables 2 & 3). For additional analyses examining potential confounds, see Supplemental results.

3.3. Amygdala regions of interest

There was a significant *diagnosis-by-animacy interaction* within left amygdala (see Table 2; Fig. 1a). TD youth showed a greater difference in BOLD response to faces to objects relative to youth with DBDs ($t = 4.724$, $p < 0.001$). There was, however, no significant group *diagnosis-by-emotion interaction* within either amygdala.

3.4. Whole brain results

3.4.1. Diagnosis-by-animacy interaction

A significant *diagnosis-by-animacy interaction* was observed within regions including left fusiform gyrus/parahippocampal gyrus, left parahippocampal gyrus, and left inferior parietal cortex/post-central gyrus (see Table 3). In all regions, a greater difference in activation to faces relative to objects was observed in TD youth compared to youth with DBDs ($ts = 4.183$–5.444, $ps \leq 0.001$).

3.4.2. Diagnosis-by-congruence interaction

A significant *diagnosis-by-congruence interaction* was observed within regions including bilateral inferior/lateral frontal cortex, right caudate, and left inferior parietal cortex (see Table 3; Fig. 2). In all regions, TD youth showed significantly greater activation during incongruent trials relative to youth with DBDs ($ts = 2.924$–4.801, $ps < 0.005$) but no significant group differences were observed during congruent trials ($ts = -0.440$–0.378, $ps > 0.707$).

3.4.3. Main effect of animacy

Regions showing a significant main effect of animacy included right fusiform gyrus, right parahippocampal gyrus, right middle occipital gyrus and left culmen (see Table 2). Right fusiform gyrus, left culmen, and right middle occipital gyrus exhibited greater activation for objects, whereas parahippocampal gyrus demonstrated greater activation for faces.

3.4.4. Main effect of emotion

Bilateral fusiform gyrus exhibited a significant main effect of emotion (see Table 2), which demonstrated greater activation for negative compared to neutral stimuli.

3.4.5. Main effect of diagnosis

Right middle frontal gyrus and left rostral anterior cingulate cortex exhibited a significant main effect of diagnosis (see Table 2), in which TD youth exhibited greater activation than youth with DBDs.

3.4.6. Other interactions

No significant interaction effects survived correction for multiple comparisons for animacy-by-congruence, emotion-by-animacy, diagnosis-by-emotion, diagnosis-by-animacy-by-congruence, emotion-by-animacy-by-congruence, or diagnosis-by-emotion-by-animacy-by-congruence interaction.

Hypothesis 2. Within the youth with DBDs, CU traits would be inversely associated with responsiveness to negative and animate stimuli within the amygdala and lateral temporal cortex.

This was examined via a 2 (animacy: faces, objects) by 2 (congruence: congruent, incongruent) by 2 (emotion: negative, neutral) repeated-measures ANCOVA with level of CU traits as the covariate was conducted within both the left and right amygdala ROIs and the whole brain for data from the participants with DBDs only. Predicted findings with respect to our ROI and whole brain results are presented below (see also, Tables 2 & 4).

3.5. Amygdala regions of interest

Notably, there was a significant *CU traits-by-animacy interaction* within right amygdala. *Higher levels* of CU traits were associated with reduced differential responses to faces ($r = -0.315$) relative to objects ($r = 0.207$, *Steiger's* $Z = 3.952$, $p < 0.001$; see Fig. 1b and Table 2). In other words, higher levels of CU traits were associated with reduced amygdala differentiation between faces and objects. In addition, a main effect of congruence was found in right amygdala when CU traits were entered as a covariate for the ANCOVA. That is, greater activation was found in response to congruent relative to incongruent ($t = 3.907$,

Table 2
Region of interest analysis of amygdala differential BOLD response during an animacy task in 29 youths with DBDs and 20 typically developing youths.

		Coordinates of peak activation[a]						
Left/right	BA	x	y	z	*F*	*p*	$\eta^2_{partial}$	Voxels
ANOVA								
Diagnosis-by-Animacy Interaction								
Left	28/36	−25.5	−4.5	−24.5	13.460	< 0.0001	0.322	5
ANCOVA								
CU traits-by-Animacy Interaction								
Right	28	25.5	−10.5	−3.5	8.538	0.0070	0.293	3
Main Effect of Congruence								
Right	28	28.5	−1.5	−18.5	8.373	0.0074	0.353	5

Note: BA = Brodmann's Area. ANOVA $n = 49$; ANCOVA $n = 29$.
[a] Based on the Tournoux & Talairach standard brain template.

Table 3
Brain regions demonstrating key significant effects and interactions from an analysis of variance on BOLD Response during an animacy task in 29 youths with DBDs and 20 typically developing youths.

Region[a]	Left/right	BA	Coordinates of peak activation[b]			*F*	*p*	$\eta^2_{partial}$	Voxels
			x	y	z				
Diagnosis-by-Animacy Interaction									
fusiform/parahippocampal gyrus	Left	36	− 37.5	− 25.5	− 12.5	14.680	< 0.0001	0.380	22
inferior parietal cortex/post-central gyrus	Left	40	− 37.5	− 34.5	47.5	14.140	< 0.0001	0.271	29
parahippocampal gyrus	Left	28	− 4.5	− 34.5	5.5	14.720	< 0.0001	0.305	22
Diagnosis-by-Congruence Interaction									
inferior/lateral frontal gyrus	Left	9	− 37.5	13.5	26.5	20.950	< 0.0001	0.360	107
inferior/lateral frontal gyrus	Right	13	37.5	− 7.5	32.5	12.030	0.0011	0.337	32
caudate	Right		10.5	4.5	2.5	12.170	0.0011	0.287	17
inferior parietal cortex	Left	40	− 43.5	− 55.5	41.5	12.130	0.0011	0.279	17
Main Effect of Animacy									
middle occipital gyrus	Right	19	31.5	− 79.5	17.5	23.760	< 0.0001	0.452	192
fusiform gyrus	Right	37	25.5	− 49.5	− 9.5	57.430	< 0.0001	0.587	378
parahippocampal gyrus	Right	28	16.5	− 10.5	− 9.5	17.760	< 0.0001	0.413	29
culmen	Left	37	− 25.5	− 40.5	− 15.5	11.270	0.0016	0.639	694
Main Effect of Emotion									
fusiform gyrus	Left	37	− 37.5	− 46.5	− 18.5	15.000	< 0.0001	0.334	57
fusiform gyrus	Right	37	40.5	− 46.5	− 12.5	13.050	< 0.0001	0.350	53
Main Effect of Diagnosis									
middle frontal gyrus	Right	47	22.5	31.5	− 3.5	14.150	< 0.0001	0.376	29
rostral anterior cingulate cortex	Left	32	− 10.5	40.5	− 3.5	12.800	< 0.0001	0.352	29

Note: BA = Brodmann's Area.
[a] According to the Talairach Daemon Atlas (http://www.nitrc.org/projects/tal-daemon/).
[b] Based on the Tournoux & Talairach standard brain template.

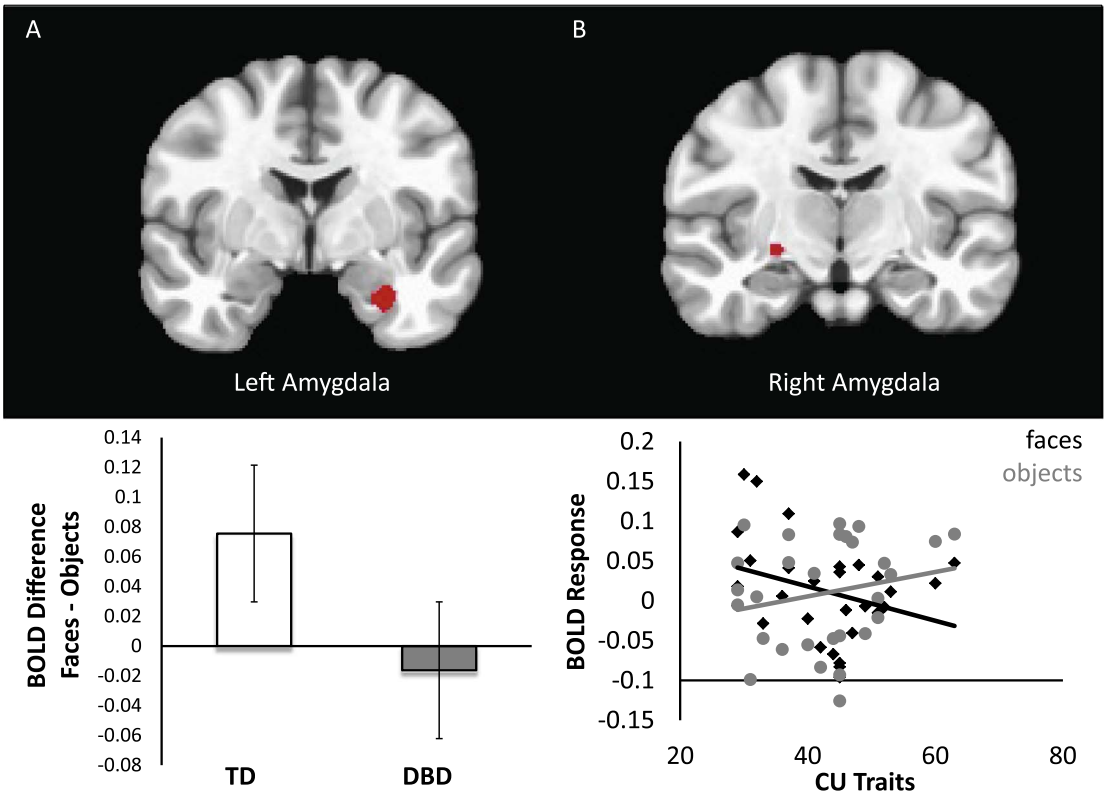

Fig. 1. Evidence of dysfunctional animacy processing in the amygdala in youth with disruptive behavior disorders.
1a. Diagnosis-by-Animacy Interaction: Greater BOLD activation difference score of faces relative to objects in TD youth (n = 20) relative to youth with DBDs (n = 29) within left amygdala. BOLD activation is shown at p = 0.005.
1b. CU traits-by-Animacy interaction: Within youth with DBDs (n = 29), greater levels of CU traits were associated with reduced responses (r = − 0.315) to faces relative to objects (r = 0.207) within right amygdala (*Steiger's Z* = 3.952, p = 0.001). BOLD activation is shown at p = 0.001.

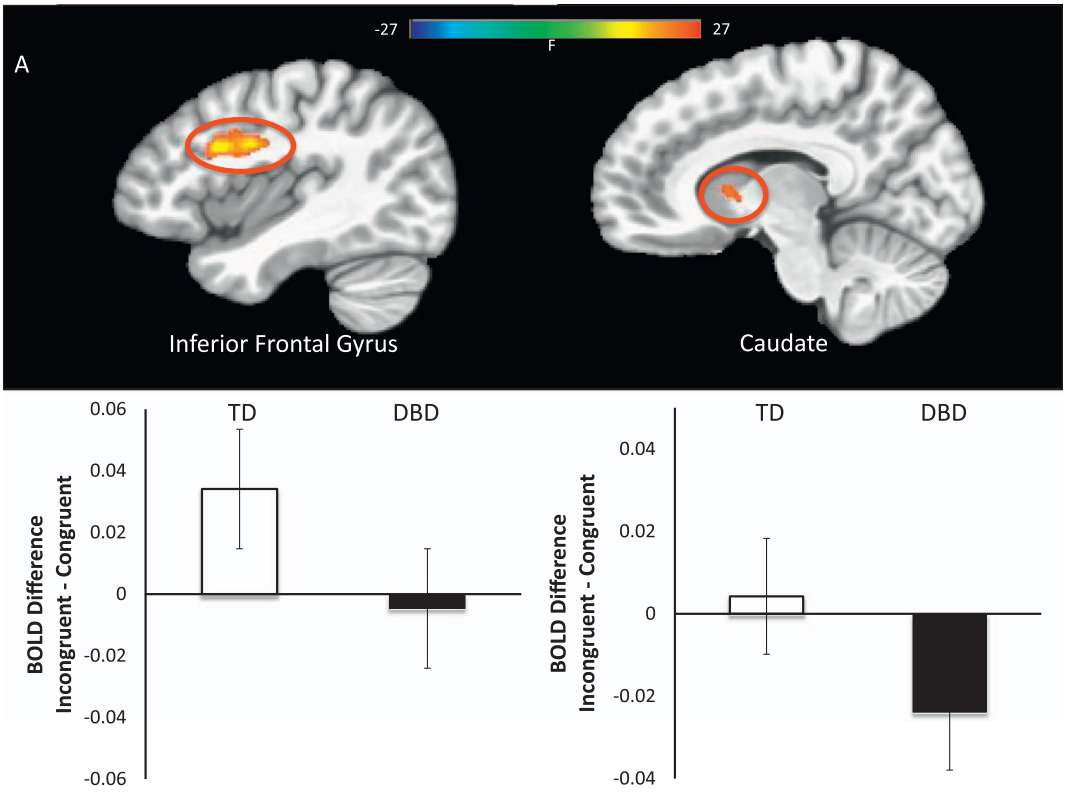

Fig. 2. Diagnosis-by-congruence interaction within response control regions.
2a. Inferior Frontal Gyrus: Youth with DBDs (n = 29) exhibited a greater difference [$F(1,47) = 26.434$, $p < 0.001$] in activation between congruent and incongruent stimuli relative to TD youth (n = 20). BOLD activation is shown at $p = 0.001$.
2b. Caudate: Youth with DBDs (n = 29) exhibited a greater difference [$F(1,47) = 18.954$, $p < 0.001$] in activation between congruent and incongruent stimuli relative to TD youth (n = 20). BOLD activation is shown at $p = 0.001$.

$p = 0.001$) stimuli.

3.6. Whole brain results

3.6.1. CU Traits-by-emotion-by-animacy interaction

Regions exhibiting significant *CU traits-by-emotion-by-animacy interactions* included right insula (see Table 4). Within this region, higher levels of CU traits were associated with reduced differential responses between negative and neutral *faces* (*Steiger's* $Z = 2.65$, $p = 0.009$), but CU traits were not associated with the difference between negative and neutral *objects* (*Steiger's* $Z = 0.637$, $p = 0.524$).

3.6.2. Main effect of animacy

Regions exhibiting a significant main effect of animacy included the left parahippocampal gyrus, right medial fusiform gyrus, and the left precentral gyrus (see Table 4). Within all regions greater activation was found in response to objects to faces ($ts = -5.133$ to -9.120, $ps < 0.001$).

3.6.3. Main Effects

No significant main effects survived correction for multiple comparisons for CU traits, congruence, or emotion.

3.6.4. Interactions

No significant interaction effects survived correction for multiple comparisons for CU traits-by-emotion, CU traits-by-congruence, CU traits-by-animacy, emotion-by-animacy, emotion-by-congruence, animacy-by-congruence, CU traits-by-congruence-by-animacy, emotion-by-congruence-by-animacy, or CU traits-by-emotion-by-congruence-by-animacy.

Table 4
Brain regions demonstrating key significant effects and interactions from an analysis of covariance on BOLD response during an animacy task utilizing callous-unemotional traits as a covariate in 29 youths with DBDs.

			Coordinates of peak activation[b]						
Region[a]	Left/right	BA	x	y	z	*F*	*p*	$\eta^2_{partial}$	Voxels
CU traits-by-Emotion-by-Animacy Interaction									
insula	Right	13	37.5	−4.5	−6.5	14.270	< 0.0001	0.491	24
Main Effect of Animacy									
parahippocampal gyrus	Left	36	−28.5	−40.5	−9.5	63.010	< 0.0001	0.748	787
medial fusiform gyrus	Right	37	25.5	−49.5	−9.5	44.790	< 0.0001	0.678	501
precentral gyrus	Left	6	−31.5	1.5	26.5	14.760	< 0.0001	0.485	21

Note: BA = Brodmann's Area.
[a] According to the Talairach Daemon Atlas (http://www.nitrc.org/projects/tal-daemon/).
[b] Based on the Tournoux & Talairach standard brain template.

3.7. Potential confounds

Over half of the youth with DBDs met criteria for attention-deficit/hyperactivity disorder (ADHD) and four youth were taking a medication that could not be withheld during scanning. Analysis removing these participants replicated the effects of interest, although some results were seen only at slightly more lenient thresholds when removing the ADHD youth from the analysis (see Supplementary results and Tables S1 and S2 in the Supplemental materials).

4. Discussion

The goal of this study was to determine whether the processing of animacy information is impaired in youth with DBDs and whether this impairment varied as a function of CU traits. There were three main findings: First, youth with DBDs showed reduced left amygdala responses to faces relative to objects compared to TD youth. Moreover, among youth with DBDs, level of CU traits was inversely related to differential responsiveness to faces relative to objects within the right amygdala. Second, youth with DBDs, relative to TD youth, showed reduced responses to faces relative to objects within temporal cortex, specifically lateral fusiform gyrus/parahippocampal gyrus, and inferior parietal cortex/post-central gyrus. Third, youth with DBDs, compared to TD youth, showed reduced responses within bilateral inferior/lateral frontal cortex and caudate in response to incongruent relative to congruent trials.

Considerable previous work has confirmed a functional role for the amygdala in processing animacy information (Cao et al., 2014; Coker-Appiah et al., 2013; Martin and Weisberg, 2003; Wheatley et al., 2007; Yang et al., 2012). Consistent with hypotheses, the current study demonstrated that this functional role is compromised in youth with DBDs. Notably, within the group of youth with DBDs, greater failure to differentiate faces and objects in amygdala responding was associated with increased CU traits. Amygdala response to animacy information is considered critical for social processing (Wheatley et al., 2007), guides individuals towards animate objects (Martin and Weisberg, 2003), and engages other cortical structures implicated in social cognition (Ochsner, 2008). The asocial behavior sometimes associated with psychopathic and CU traits is possibly a function of this reduced amygdala response to animacy information. These individuals may be insensitive to the salience of animate conspecifics, which may contribute to these youths' disrupted socialization (Frick et al., 2014; Frick and White, 2008).

There are considerable interconnections between the amygdala and lateral temporal cortex (Aggleton, 2000). Further, lateral temporal cortex shows increased responsiveness to animate relative to inanimate stimuli (Caramazza and Shelton, 1998; Martin, 2007). Here, we observed that youth with DBDs showed reduced responses, relative to TD youth, to faces relative to objects within the amygdala and lateral fusiform gyrus; areas identified as particularly responsive to animate stimuli (Caramazza and Shelton, 1998; Martin, 2007). This strengthens the suggestion that animacy processing is compromised in youth with DBDs. It should be noted, however, that CU traits in the youth with DBDs were not associated with reduced responsiveness to faces within lateral temporal cortex. This is somewhat surprising given the theoretical role of amygdala in directly priming activation to animate stimuli in this region and the reduced amygdala response to animate stimuli observed as a function of CU traits in the current study.

The significant diagnosis-by-congruence interactions within bilateral inferior/lateral frontal cortex and caudate are interesting. Within these regions, the difference between BOLD responses to incongruent relative to congruent stimuli was significantly greater in TD youth relative to DBDs youth. Inferior/lateral frontal cortex and caudate have been implicated in response inhibition/control (Aron, 2011; Aron et al., 2003; Cai and Leung, 2011; Chikazoe et al., 2009; Dodds et al., 2011; Meffert et al., 2016). Healthy individuals show greater recruitment of these regions during no-go trials on go/no-go paradigms (e.g., Chikazoe et al., 2009; Meffert et al., 2016) and during incongruent relative to congruent trials on paradigms similar to the current one (e.g., Blair et al., 2007; Krebs et al., 2015; Price et al., 2014). An association between dysfunctional response inhibition and externalizing behaviors (Patrick et al., 2013; Young et al., 2009), particularly impulsivity (Krueger et al., 2007; Loeber et al., 2009), has repeatedly been made. The current imaging results would be consistent with this suggestion, although it should be noted that the groups did not differ in behavioral performance. The imaging results are also consistent with claims that some youth with DBDs may show a form of pathophysiology related to dysfunction in systems implicated in response inhibition that does not manifest as CU symptomatology, but rather as impulsiveness (Blair, 2013; for similar findings see Hwang et al., 2016). Although impulsive symptomatology was not assessed in the participants in the current study, the argument above stresses that it may be useful to do so in future work (c.f. Hwang et al., 2016).

The current data need to be considered in light of six caveats. First, and most importantly, the current data were interpreted in terms of reduced responsiveness to animacy in youth with DBD. However, the stimuli used here were prototypically animate (Gobbini et al., 2011; Yang et al., 2012), specifically faces. As such, it is possible that the difficulty faced by youth with DBD and elevated CU traits is in responding to fearful face stimuli rather than animate stimuli more generally. Future work will need to specify the specificity of the dysfunction by examining responsiveness to animals relative to objects (Coker-Appiah et al., 2013; Yang et al., 2012) and inanimate objects moving in animate ways (Martin and Weisberg, 2003; Wheatley et al., 2007). Second, the predicted reduced amygdala response to emotional (i.e., fearful) stimuli in youth with DBDs or any significant association between amygdala response to emotional stimuli and CU traits in the youth with DBDs was not observed. Such a result is inconsistent with previous work (Hwang et al., 2016; Marsh et al., 2008; Viding et al., 2012; White et al., 2012a). Reduced responses to (animate) emotional stimuli in the youth with DBDs were observed and responsiveness to these stimuli was inversely associated with level of CU traits. However, these findings were in the insula, which engages in attentional control/salience detection, not the amygdala (see Table 4). We thus assume the failure to observe a reduced amygdala response to threat stimuli in the youth with DBDs reflects type II error. Notably, in this study the TD youth did not show a significant emotion effect within the amygdala (see Tables 2 and 3), despite copious work demonstrating amygdala responsiveness to emotional stimuli including facial expressions (Gobbini et al., 2011; Pessoa and Adolphs, 2010; Yang et al., 2012), threatening animals (Cao et al., 2014; Coker-Appiah et al., 2013; Mobbs et al., 2010; Yang et al., 2012) and threatening objects (Cao et al., 2014; Coker-Appiah et al., 2013; Wheatley et al., 2007; White et al., 2014; Yang et al., 2012). We are uncertain why this occurred. It may reflect a chance result. Alternatively, it may reflect parameters of the current paradigm; indeed TD youth failed to show amygdala responses to emotional stimuli in another emotion-attention paradigm (White et al., 2012b). Third, although the animacy attention tasks utilized both faces and objects, no non-human animate images were presented as stimuli. Fourth, an ADHD-only comparison group was not included. Fifth, four youth with DBDs were scanned while taking medications that could not be withheld. However, mitigating both these latter limitations, secondary analyses excluding youth with ADHD and youth taking medications did not fundamentally change the results. Sixth, DBDs symptom severity levels were not available for the sample, preventing examination of the effect of CU traits at given levels of symptom severity. Furthermore, neither maltreatment history, nor socioeconomic status data were available for the sample. However, it should be noted that maltreatment (for a review see McCrory et al., 2017) and socioeconomic status (for a meta-analysis see Hein and Monk, 2016) have been consistently shown to be associated with increased, rather than decreased, responsiveness to threat stimuli. Although it is possible that

maltreatment and low socioeconomic status could increase amygdala responsiveness to threat but decrease amygdala responsiveness to animacy information, we consider this possibility unlikely. However, future work should indeed assess these variables so that their contribution can be determined.

In summary, these data indicate that youth with DBDs show impairment in processing animacy information within the amygdala. Critically, this impairment is associated with greater levels of CU traits. Thus, this study provides evidence of amygdala impairment beyond the processing of emotion information in youth with DBDs. This reduced responding to faces may underlie the relationship between CU traits and clinically relevant, asocial behaviors, like not enjoying or valuing relationships. Furthermore, these findings may impact treatment. In particular, these data suggest that animacy responsiveness together with emotional responsiveness might be a treatment target for interventions addressing DBDs and CU traits. Additionally, the observed impaired recruitment of regions implicated in response inhibition in youth with DBDs suggests that this form of dysfunction should be a treatment target for at least some youth with DBDs. As such, the current study identifies several specific and partially independent treatment targets, an important preliminary step on the path to designing individualized treatment strategies for youth with DBDs.

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Conflict of interest

All authors report no biomedical financial interests or potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2017.08.024.

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