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Neural processing of socioemotional content in conduct-disordered juvenile offenders with limited prosocial emotions

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ABSTRACT

Background: Reflecting evidence on Callous-Unemotional (CU) traits (e.g., lack of empathy and guilt, shallow affect), the DSM-5 added a categorical CU-based specifier for Conduct Disorder (CD), labeled 'with Limited Prosocial Emotions' (LPE). Theory and prior work suggest that CD youths with and without LPE will likely differ in neural processing of negative socioemotional content. This proposition, however, is mainly derived from studies employing related, yet distinct, operationalizations of CU traits (e.g., dimensional measure/median split/top quartile), thus precluding direct examination of LPE-specific neurocognitive deficits.

Methods: Employing a DSM-5 informed LPE proxy, neural processing of recognizing and resonating negative socioemotional content (angry and fearful faces) was therefore examined here among CD offenders with LPE (CD/LPE+; $N = 19$), relative to CD offenders without LPE (CD/LPE-; $N = 31$) and healthy controls (HC; $N = 31$).

Results: Relative to HC and CD/LPE- youths and according to a linearly increasing trend (CD/LPE- < HC < CD/LPE+), CD/LPE+ youths exhibited hyperactivity within dorsolateral, dorsomedial, and ventromedial prefrontal regions during both emotion recognition and resonance. During emotion resonance, CD/LPE+ youths additionally showed increased activity within the posterior cingulate and precuneal cortices in comparison to HC and CD/LPE- youths, which again followed a linearly increasing trend (CD/LPE- < HC < CD/LPE+). These effects moreover seemed specific to the LPE specifier, when compared to a commonly employed method for CU-based grouping in CD (i.e., median split on CU scores).

Conclusions: These data cautiously suggest that CD/LPE+ youths may exhibit an over-reliance on cortical neurocognitive systems when explicitly processing negative socioemotional information, which could have adverse downstream effects on relevant socioemotional functions. The findings thus seem to provide novel, yet preliminary, clues on the neurocognitive profile of CD/LPE+, and additionally highlight the potential scientific utility of the LPE specifier.

1. Introduction

Conduct Disorder (CD) is a severe and difficult to treat psychiatric disorder of childhood and adolescence, characterized by a pervasive pattern of aggressive and antisocial behaviors. A widely shared concern is that CD is too heterogeneous in terms of etiology, severity, and treatment responsiveness, to be useful to researchers and clinicians (Lahey, 2014). For this reason, DSM-5 added a new specifier for the diagnosis of CD, labeled 'with Limited Prosocial Emotions' (LPE), which is largely rooted in research on Callous-Unemotional (CU) features of the psychopathy construct (APA, 2013b). This LPE specifier is employed when an individual with CD exhibits two or more of the

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following criteria: (a) lack of remorse or guilt, (b) callous–lack of empathy, (c) shallow or deficient affect, and (d) unconcerned about performance (APA, 2013b). The main purpose of the LPE specifier is providing researchers and clinicians with a standardized and broadly agreed upon methodology for identifying high-risk CD youths, who may need differential clinical care due to distinct neurocognitive deficits and etiological pathways (Frick et al., 2014; Kimonis et al., 2015). The specifier is, for instance, deemed capable of identifying CD youths with specific impairments in neural processing of negative socioemotional content (Blair et al., 2014; Blair, 2013a; Frick et al., 2014), which ostensibly underpins their antisocial tendencies to a large extent.

Most evidence on LPE pathophysiology, however, has been indirect and derived from studies that used related, yet distinct, operationalizations of CU traits (e.g., dimensional measure/median split/top quartile), thus precluding direct examination of LPE-specific neurocognitive deficits. In fact, the only neurobiological study to date that has utilized a DSM-5 informed LPE proxy in CD diagnosed teens focused exclusively on white matter integrity (i.e., structural connectivity), without explicitly probing socioemotional neural processing (Sethi et al., 2018b). So, while prior work has been imperative in establishing a rationale for developing the LPE specifier, studies are urgently needed to evaluate its clinical and scientific utility, as well as its neurocognitive profile. Using a DSM-5 informed LPE proxy, we therefore probed neural processing of recognizing and resonating negative socioemotional content (angry and fearful faces) among CD offenders with LPE, relative to CD offenders without LPE and healthy controls.

Emotion recognition refers to the capacity to infer someone else's emotional state from facial expression, whereas emotion resonance refers to the capacity to share or become affectively aroused by others' emotional states. Various studies among youths with conduct problems have examined the impact of CU traits on emotion recognition, and with some notable exceptions (Fairchild et al., 2010; Fairchild et al., 2009; Schwenck et al., 2012; Sully et al., 2015), they collectively link elevated CU levels to difficulties in recognizing negative emotions, such as fear, sadness, and anger (Baker et al., 2015; Blair et al., 2014; Dawel et al., 2012; Frick et al., 2014). Importantly, while some studies hint at preserved cognitive understanding of emotions in antisocial youths with CU traits, the ability of affectively responding to and share other's emotions seems significantly hampered (Blair et al., 2014; Blair, 2013a). It is noteworthy that antisocial youths without CU characteristics typically showcase the *opposite* processing pattern, including *hyperresponsivity* to negative affective stimuli that additionally impedes their cognitive understanding of others' emotions (Blair et al., 2014; Blair, 2013a). Interestingly, while preserved cognitive-emotional understanding and lack of affective contagion/resonance in high CU youths conjointly promote proactive/instrumental aggression, their low CU peers seem more susceptible to reactive aggression due to emotional hyperresponsivity/dysregulation (Blair et al., 2014; Blair, 2013a).

The impairments in recognizing/resonating emotions in high CU populations are tentatively ascribed to perturbations within cortico-paralimbic circuits that serve various aspects of emotion processing (Anderson and Kiehl, 2014; Blair et al., 2014; Blair, 2013a; Viding and McCrory, 2012). Specifically, (para)limbic circuits accommodating emotional arousal and awareness (e.g., amygdala and insula) seem hyporesponsive to negative affective stimuli, while cortical neurocognitive systems (prefrontal, cingulate, and parietal cortices) tend to function at normal to excessive degrees (Alegria et al., 2016; Anderson and Kiehl, 2012; Anderson et al., 2017; Blair et al., 2014; Blair, 2013a; Contreras-Rodriguez et al., 2014; Decety et al., 2013a; Decety et al., 2015; Decety et al., 2014; Decety et al., 2013b). In addition, the interconnectivity within these cortico-paralimbic circuits appears largely imbalanced and atypical, with both perturbed network functional cross-talk and white matter disorganization being reported (Aghajani et al., 2016; Aghajani et al., 2018; Aghajani et al., 2017; Alegria et al., 2016; Anderson and Kiehl, 2012; Anderson et al., 2017; Blair et al., 2014; Blair, 2013a; Blair et al., 2018; Contreras-Rodriguez et al., 2014; Waller et al., 2017).

These factors are believed to collectively bias salience processing and attentional encoding, prompting subsequent impairments in affective reactivity and emotional learning (Blair, 2013a; Contreras-Rodriguez et al., 2014; Decety et al., 2013a; Decety et al., 2015; Decety et al., 2014; Decety et al., 2013b). Noteworthy, antisocial youths *lacking CU* features tend to generally exhibit the *opposite* neuroaffective patterns when recognizing or resonating negative socioemotional content (Alegria et al., 2016; Anderson and Kiehl, 2014; Blair et al., 2016; Blair, 2013a). Crucially though, no study has yet examined the impact of CU traits, as categorically defined by the DSM-5 LPE specifier, on these emotional processes and their putative neural circuitry. This is of relevance, for it may allow deeper insights into the clinical and scientific utility of this new DSM-5 subtyping scheme for CD, as well as its underlying pathophysiology.

2. Current study

Employing a DSM-5 informed LPE proxy, neural processing of recognizing and resonating negative socioemotional content was therefore examined here among CD offenders with LPE (CD/LPE+; $N = 19$), relative to CD offenders without LPE (CD/LPE-; $N = 31$) and healthy controls (HC; $N = 31$). During this task, participants were presented with angry and fearful facial expressions, and had to infer the emotional state from the face (emotion recognition) or feel into/empathize with the emotional face and judge their own emotional response to it (emotion resonance).

We hypothesized reduced (para)limbic (amygdala, insula, striatum) activity and excessive cortical (prefrontal, cingulate, and parietal cortices) recruitment in CD/LPE+ youths versus HC and CD/LPE- participants, a pattern deemed indicative of over-reliance on cognitive (controlled) processes to compensate for intrinsic affective deficits (Anderson et al., 2017; Contreras-Rodriguez et al., 2014; Decety et al., 2013a; Decety et al., 2015; Decety et al., 2014; Decety et al., 2013b; Glenn et al., 2009; Sadeh et al., 2013; Yoder et al., 2015a; Zijlmans et al., 2018). We speculated the group differences to follow a linear trend, wherein CD/LPE+ and CD/LPE- youths would each represent opposing ends of a continuum, with HC youths in the middle representing the reference point (i.e., CD/LPE- $\gtrless$ HC $\gtrless$ CD/LPE+). As mentioned earlier, opposing neuroaffective responses to distressing emotions have been tentatively suggested in CD youths with high vs. low CU levels, both in comparison to each other, as well as to HC youths (Alegria et al., 2016; Anderson and Kiehl, 2014; Anderson et al., 2017; Blair et al., 2016; Blair, 2013a). Exploratory analyses additionally tested quadratic trends that treated CD/LPE+ and CD/LPE- youths as equals in comparison to HC youths (CD/LPE- $\gtrless$ HC $\lesseqgtr$ CD/LPE+), to elucidate possible commonalities among CD youths in general.

3. Methods & materials

3.1. Participants

Fifty severely antisocial male juvenile offenders with a DSM-5 diagnosis of CD (mean age = 16.84, *SD* = 1.25) and 31 healthy control males (mean age = 17.02, *SD* = 1.18) were included, all group-level matched on age and IQ. Participants were part of a larger study on the effects of juvenile antisocial, psychopathic, and autistic tendencies on socioemotional brain systems (Aghajani et al., 2016; Klapwijk et al., 2017). All participants were aged 15 to 19 years old and medication-free, with psychotropic medication use being a study exclusion criterium. Juvenile offenders with CD were recruited from a juvenile detention center and a forensic psychiatric facility, and had all been convicted for or charged with crimes such as assault, murder, and armed robbery. Healthy controls were carefully recruited through local advertisement. The medical ethics committee of the Leiden University Medical Center approved the study and written informed consent was obtained from all adolescents and their parents. All methods and procedures were performed in accordance with the approved guidelines of the ethics committee. More details regarding participant inclusion are provided in the Supplement.

3.2. Classification measures

3.2.1. DSM-5 CD

Diagnoses of CD were confirmed using a commonly employed semi-structured diagnostic interview (K-SADS; see Supplement). In line with prior work (Aghajani et al., 2016), CD youths had to fulfill criteria for CD with at least one aggressive CD symptom (e.g., has been physically cruel to people), which tends to identify a more homogenous group of severely antisocial CD youth.

3.2.2. DSM-5 LPE Specifier

One of the most frequently used tools in studies on the DSM-5 LPE specifier among criminal justice-involved CD youths is the Youth Psychopathic Traits Inventory (YPI) (Colins, 2016; Colins and Andershed, 2015; Colins and Vermeiren, 2013). This tool has adequate validity and reliability (Colins et al., 2017; Neumann and Pardini, 2014; Pihet et al., 2014; Poythress et al., 2006) and commonly used in neurobiological studies of juvenile antisociality/psychopathy (Aghajani et al., 2016; Cohn et al., 2014; Fairchild et al., 2013; Marsh et al., 2008).

Following prior work (Colins, 2016; Colins and Andershed, 2015; Colins and Vermeiren, 2013; Jambroes et al., 2016) the YPI Callous-Unemotional domain and its subscales were used to probe LPE criterions (see Fig. 1). The Callous-Unemotional subscale Remorselessness (comprised of five individual items probing remorse) was used to assess the LPE specifier criterion “lack of remorse or guilt”. The Callous-Unemotional subscale Callousness (comprised of five individual items probing callous tendencies) was used to assess the LPE specifier criterion “callous-lack of empathy”. The Callous-Unemotional subscale Unemotionality (comprised of five individual items probing unemotional responses) was used to assess the LPE specifier criterion “shallow or deficient affect”. The scoring range for the individual items probing each criterion was 1 to 5.

In line with prior studies that used the YPI to assess the DSM-5 LPE specifier (Colins, 2016; Colins and Andershed, 2015; Colins and Vermeiren, 2013; Jambroes et al., 2016), CD youths would meet a specific LPE *criterion* (i.e., lack of remorse or guilt/callous-lack of empathy/shallow or deficient affect) if they had the maximum score of 5 on at least one out of the five individual items of that specific criterion. Following DSM-5 guidelines, youths were considered to fulfill the LPE specifier (i.e., CD/LPE+) if they met *at least two* of the above-mentioned LPE criterions (Colins and Andershed, 2015; Colins and Vermeiren, 2013). Based on these criteria, 19 out of the 50 CD youths met the criteria for the LPE specifier (CD/LPE+: $N = 19$ & CD/LPE-: $N = 31$; see Table 1 for characteristics). Of note, none of the included HC youth ($N = 31$) met criteria for the LPE specifier. The total specifier score, denoting the number of individual criterion items on which a given participant had the maximum score of 5, was also calculated as an indicator of LPE severity (15 items, scoring range 0–15). The YPI Callous-Unemotional total sore was also calculated, which simply sums up the participant scores on the 15 individual criterion items (15 items, Likert scale 1–5, total scoring range 15–75).

3.3. Emotional processing task

An explicit socioaffective processing task used previously to probe neural underpinnings of CU and autistic traits was employed (e.g., Aghajani et al., 2018; Greimel et al., 2010; Klapwijk et al., 2016; Schulte-Ruther et al., 2014) (Fig. 2). Distressing facial expressions (i.e., angry and fearful) of ethnically diverse young men were presented, and participants were explicitly asked to either infer the emotional state from the face (proxy for emotion recognition) or feel into/empathize with the emotional face and judge their own emotional response to it (i.e., proxy for emotion resonance). A perceptual decision on the width of neutral faces was included as control condition (see Supplement for detailed task description).

3.4. fMRI data acquisition and preprocessing

A Philips Achieva 3 T MRI scanner was used to collected task-fMRI data. All data were subjected to standard preprocessing steps, using FSL version 5.0.9 (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Motion-censoring was additionally implemented to guard against the effects of in-scanner micro-motion (Siegel et al., 2014), which on its own tends to outperform other motion correction strategies for task-fMRI data, with the addition of extra motion parameters (e.g., 24|36) not further improving BOLD response estimates (Siegel et al., 2014). We also used padding and restraint during MRI to minimize head-motion, and excluded participants with mean head motion above 3^{mm} translation|3° rotation to mitigate motion-related effects. For more detail on data acquisition and preprocessing see Supplement.

3.5. fMRI data analysis

First, subject-level statistical analyses using FILM with local autocorrelation correction were performed in FEAT. This entailed a general linear model (GLM) wherein regressors for each condition were convolved with a double-gamma hemodynamic response function, while contrasts testing for neural responses to emotion recognition (emotion recognition > control) and emotion resonance (emotion resonance > control) were constructed. Importantly, the six motion parameters (i.e., mean relative displacement measures) and parameters obtained from the motion censoring procedure (see Supplement for details) were also included in this model to correct for residual motion-related variance (Siegel et al., 2014).

All subject-level statistical maps were subsequently fed into a single mixed-effects multivariate GLM group-analysis (whole-brain) implemented in FEAT, using the sophisticated Bayesian modeling and estimation method FLAME 1 + 2 (with automatic outlier deweighting). To test our hypothesis of linearly decreasing/increasing activity in CD/LPE+ youths relative to HC and CD/LPE- youths, respectively, two linear contrasts were tested within the GLM analyses: a) CD/LPE- > HC > CD/LPE+, b) CD/LPE- < HC < CD/LPE+. To pinpoint possible commonalities in neural activity between CD/LPE+ and CD/LPE- youths in comparison to HC youths, two exploratory quadratic trends were additionally tested: a) CD/LPE- > HC < CD/LPE+ b) CD/LPE- < HC > CD/LPE+. These quadratic trends treat CD/LPE+ and CD/LPE- youths as equals in the GLM, and basically compare the combined CD/LPE+ & CD/LPE- group to the HC group, testing for an (inverted)U-shape trend. Inter-individual variance in age and IQ was adjusted for in these analyses. Statistical images were non-parametrically thresholded and family-wise error corrected, using an initial cluster-forming threshold of $Z > 2.3$ and a cluster significance level of $P < 0.01$, which in combination with FLAME 1 + 2 robustly balances the rates of false positives and negatives.

4. Results

4.1. Sample characteristics

As shown in Table 1, CD/LPE+ youths were characterized by higher levels of CU traits (i.e. YPI CU scale), aggressive tendencies, rule-breaking behavior, externalizing symptomology, along with decreased empathy and low socioeconomic status. The groups importantly did not differ on levels of in-scanner head motion.

Proposed DSM-5 LPE Criterions	Criterion 1 Lack of remorse or guilt	Criterion 2 Callous lack of empathy	Criterion 3 Shallow or deficient affect
Step 1: YPI items to probe DSM-5 LPE criterions	**YPI Remorselessness** *Subscale Items*	**YPI Callousness** *Subscale Items*	**YPI Unemotionality** *Subscale Items*
	To feel guilty and remorseful about things you have done that have hurt other people is a sign of weakness. I have the ability not to feel guilt and regret about things that I think other people would feel guilty about. When someone finds out about something that I've done wrong, I feel more angry than guilty. To feel guilt and regret when you have done something wrong is a waste of time. I seldom regret things I do, even if other people feel that they are wrong.	I usually become sad when I see other people crying or being sad (reverse). Important to me not to hurt other people's feelings (reverse). I often become sad or moved by watching sad things on TV or film (reverse). When other people have problems, it is often their own fault; therefore, one should not help them. I think that crying is a sign of weakness, even if no one sees you.	I usually feel calm when other people are scared. What scares others usually doesn't scare me. To be nervous and worried is a sign of weakness. I don't let my feelings affect me as much as other people's feelings seem to affect them. I don't understand how people can be touched enough to cry by looking at things on TV or movie.
Step 2: DSM-5 LPE criterion met?	**Yes, if at least one item does apply very well (score of 5)**	**Yes, if at least one item does apply very well (score of 5)**	**Yes, if at least one item does apply very well (score of 5)**
Step 3: DSM-5 LPE specifier met?	**Yes, if two or more DSM-5 LPE criterions are met**		

Fig. 1. Schematic representation of the step-wise methodology employed to assess the presence of the DSM-5 LPE specifier, using the YPI Callous-Unemotional subscale items. The Remorselessness, Callousness, and Unemotionality subscales from the Callous-Unemotional domain of the YPI were used, which probe the LPE criterions "lack of remorse or guilt", "callous-lack of empathy", and "shallow or deficient affect", respectively. Following DSM-5 guidelines, CD youths were considered to fulfill the LPE specifier if they met *at least two* of the above-mentioned LPE criterions.

4.2. Behavioral data

Consonant with the fMRI analyses, multivariate analysis of covariance (MANCOVA) tested for linearly or quadratically increasing/decreasing group effects in task reaction times (RT). In the analysis, group was the between-subject factor and task conditions' RT's the dependent variables, with age and IQ additionally included as covariates. The analyses revealed no linearly increasing/decreasing group effects ($P's > 0.05$), meaning the groups did not differ in RT's during the 3 task conditions (recognition/resonance/control) according to a linear trend. The analysis did point to a quadratic group effect, wherein both CD groups exhibited faster RT's than HC youth during emotion resonance (CD/LPE+: $M = 1066.34$, $SE = 57.93$; HC: $M = 1339.65$, $SE = 44.60$; CD/LPE-: $M = 1141.87$, $SE = 44.57$; Univariate Model $F(2,76) = 8.35$, $P < 0.001$; Quadratic Contrast: 95% CI = −286.35 – -98.30, $P < 0.001$). Post-hoc tests further delineated the quadratic effect: HC vs. CD/LPE+: Mean difference(SD) = 273.31 ± (73.74), $P < 0.001$ | HC vs. CD/LPE-: Mean difference (SD) = 197.78 ± (62.94), $P < 0.01$.

Multivariate analyses additionally probed for linearly or quadratically increasing/decreasing group effects in percentage of correct responses during emotion recognition, as well as percentage of congruent emotions reported during emotion resonance. No group differences emerged on correct attribution of other's emotions (CD/LPE+ = 80%; HC = 82%; CD/LPE- = 80%, $P's > 0.05$), or level of congruency with other's emotional state (CD/LPE+ = 21%; HC = 20%; CD/LPE- = 18%, $P's > 0.05$).

4.3. fMRI data

Across groups, the emotion conditions elicited a network of cortico-paralimbic brain regions, including prefrontal, cingulate, insular, parietal, and temporal cortices, along with the amygdala, hippocampus, and striatum. Our contrasts of interest importantly revealed between-group differences in neural activity levels during task performance. Relative to HC and CD/LPE- youths and according to a linearly increasing trend (CD/LPE- < HC < CD/LPE+), CD/LPE+ youth exhibited hyperactivity within dorsolateral, dorsomedial, and ventromedial prefrontal regions during both emotion recognition and resonance (Figs. 3, 4 and Table S1, S2). During emotion resonance, CD/LPE+ youth additionally showed increased activity within the posterior cingulate and precuneal cortices in comparison to HC and CD/LPE- youths, which again followed a linearly increasing trend (CD/LPE- < HC < CD/LPE+) (Fig. 4 and Table S2).

To conduct post-hoc exploratory analyses, FSL's FEATquery tool was used to extract subject-level neural response estimates (i.e., mean z-values) within brain clusters showing linear group effects, which were then further analyzed within SPSS (SPSS V.22; IBM Corp, Armonk, NY).

Table 1
Characteristics of the sample.

Characteristic	CD/LPE+	CD/LPE-	HC	Difference
	N = 19	*N* = 31	N = 31	
Age (Mean ± SD) [ns]	16.43 ± 1.10	17.09 ± 1.29	17.02 ± 1.18	
IQ (Mean ± SD) [ns]	95.95 ± 7.10	96.29 ± 6.05	97.68 ± 9.64	
SES (N) [a], [**]	12/3/4	13/11/7	4/11/16	1 = 2 < 3
YPI—CU (Mean ± SD) [***]	42.27 ± 7.92	28.45 ± 4.61	26.90 ± 4.11	1 > 2 = 3
LPE Total (Mean ± SD) [***]	6.37 ± 3.45	1.07 ± 0.93	0.90 ± 0.77	1 > 2 = 3
RPQ—Reactive (Mean ± SD) [**]	13.21 ± 5.19	9.95 ± 4.31	6.65 ± 3.06	1 > 2 > 3
RPQ—Proactive (Mean ± SD) [**]	9.73 ± 6.14	4.97 ± 4.53	1.45 ± 1.73	1 > 2 > 3
BES (Mean ± SD) [***]	60.11 ± 10.15	68.97 ± 10.13	74.65 ± 8.93	1 < 2 < 3
YSR—Rule Breaking (Mean ± SD) [**]	10.22 ± 3.80	5.90 ± 4.05	3.87 ± 1.91	1 > 2 > 3
YSR—Externalizing (Mean ± SD) [**]	18.67 ± 9.59	10.97 ± 7.81	7.53 ± 4.21	1 > 2 > 3
YSR—Internalizing (Mean ± SD) [*]	8.78 ± 3.90	4.83 ± 4.14	7.17 ± 5.06	1 > 2 < 3
Substance use frequency (N) [b], [ns]	6/5/8	12/7/12	16/11/4	
Comorbid ADHD (N) [ns]	5	6		
Motion parameters				
Translation (mm)				
- X (Mean ± SD) [ns]	0.02526 ± 0.12244	0.00314 ± 0.04385	0.00232 ± 0.08414	
- Y(Mean ± SD) [ns]	0.03800 ± 0.15038	−0.00888 ± 0.12536	0.00546 ± 0.15534	
- Z (Mean ± SD) [ns]	0.03479 ± 0.30905	0.05230 ± 0.44352	−0.03577 ± 0.31412	
Rotation (°)				
- Pitch (Mean ± SD) [ns]	0.00139 ± 0.00646	−0.00031 ± 0.00663	0.00072 ± 0.00699	
- Roll (Mean ± SD) [ns]	−0.00138 ± 0.00367	−0.00009 ± 0.00170	−0.00080 ± 0.00282	
- Yaw (Mean ± SD) [ns]	0.00075 ± 0.00181	−0.00015 ± 0.00099	−0.00008 ± 0.00187	

CD/LPE+ = Conduct Disorder with Limited Prosocial Emotions; CD/LPE- = Conduct Disorder without Limited Prosocial Emotions; HC = Healthy Controls; IQ = Intelligence quotient; SES = Socioeconomic status; YPI—CU = Youth Psychopathic Traits Inventory—Callous-Unemotional scale; LPE Total = Limited Prosocial Emotions total score, indicating the number of LPE criterion items with a maximum score (continuous variable; 0–15); RPQ—Reactive = Reactive-Proactive Aggression Questionnaire—Reactive subscale; RPQ—Proactive = Reactive-Proactive Aggression Questionnaire—Proactive subscale; BES = Basic Empathy Scale; YSR—Rule-breaking = Youth Self-report—Rule-breaking subscale; YSR—Externalizing = Youth Self-Report—General Externalizing Symptomology; YSR—Internalizing = Youth Self-Report—General Internalizing Symptomology; ADHD = Attention Deficit Hyperactivity Disorder. Note: 4 participants did not complete the YSR questionnaire (CD/LPE+ *N* = 1; CD/LPE- *N* = 2, HC N = 1).

[a] SES (Low/Middle/High).
[b] Substance use in the past month (Never-Rarely/Occasionally/Very Frequently).
[*] Significant at $p < 0.05$.
[**] Significant at $p < 0.01$.
[***] Significant at $p < 0.001$.
[ns] Not significant at $p < 0.05$.

The analyses revealed that brain activity shifts in CD/LPE+ relative to HC and CD/LPE- were not confounded by comorbidity, substance use, socioeconomic status, CD severity, internalizing symptomatology, and inter-individual variance in behavioral task performance (all P's < 0.05, see sensitivity analyses in Supplement). Bivariate correlation analyses additionally revealed that neural activity within

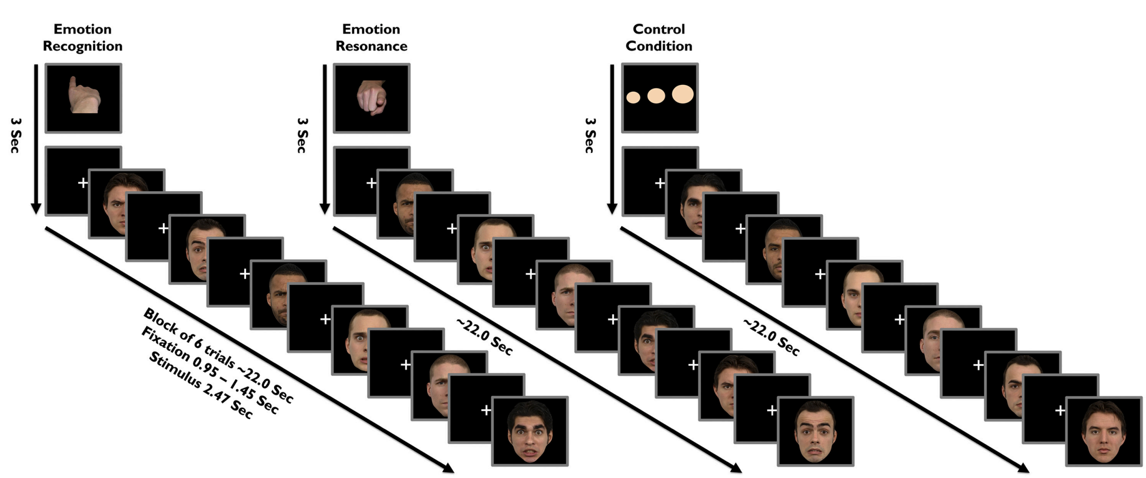

Fig. 2. Time course of stimulus presentation during scanning session. Negative facial expressions (i.e., angry and fearful) of ethnically diverse young men were presented, and participants were either asked to infer the emotional state from the face (i.e., emotion recognition) or feel into/empathize with the emotional face and judge their own emotional response to it (i.e., emotion resonance). In the high-level control condition, subjects judged the width of neutral faces (thin, normal, or wide). Each block (~22.0 s) was preceded by an instruction cue (3 s), and comprised six face trials (each 2.47 s), separated by a fixation cross (jittered 0.95–1.45 s). Twelve blocks of each task were presented in quasi-random order, resulting in 36 blocks. To avoid habituation effects and predictable stimulus sequences, emotion categories (i.e., anger and fear) were mixed within blocks. Instruction cues were pictures of a finger pointing away from the subject (emotion recognition), pointing towards the subject (emotion resonance), or three dots of increasing width (control condition).

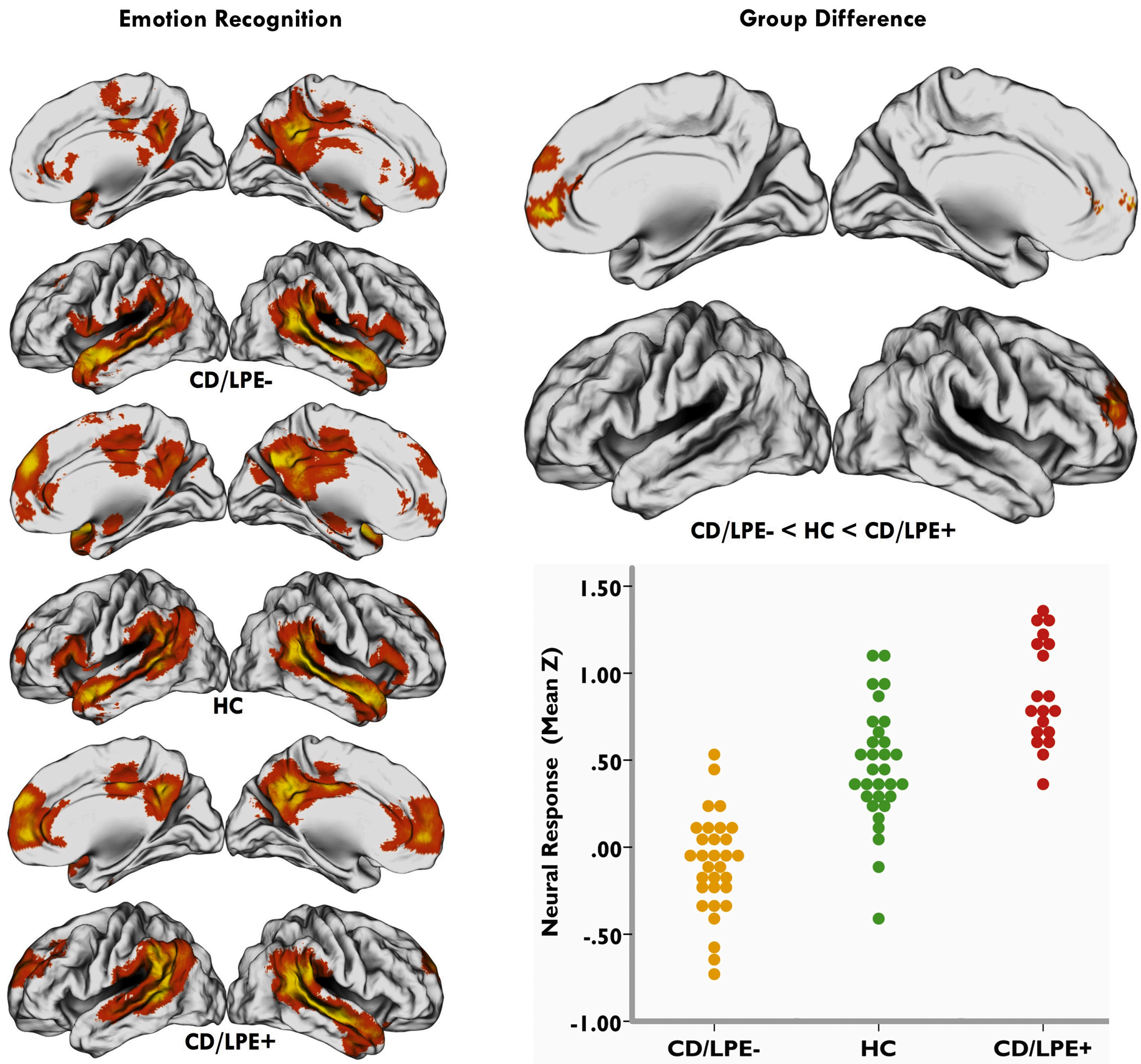

Fig. 3. Cortical hyperactivity during emotion recognition in CD/LPE+. The left panel depicts medial and lateral views of brain regions activated during emotion recognition in CD/LPE- (upper row), HC (middle row), and CD/LPE+ (lower row) participants. Relative to HC and CD/LPE- youths and according to a linearly increasing trend (CD/LPE- < HC < CD/LPE+), CD/LPE+ youth exhibited hyperactivity within dorsolateral, dorsomedial, and ventromedial prefrontal regions during emotion recognition (right panel upper row). The distribution plot (right panel lower row) provides a quantitative visualization of this linear effect, wherein neural response estimates (y axis) as indexed by z-values averaged across all illuminated voxels are plotted for each group (x axis). FSL's FEATquery tool was used to extract these subject-level neural response estimates (i.e., mean *Z*-values) within depicted brain clusters showing the linear group effect. All statistical maps are non-parametrically thresholded and family-wise error corrected (threshold $Z > 2.3$, significance $P < 0.01$). CD/LPE+ = conduct disorder with Limited Prosocial Emotions; CD/LPE- = conduct disorder without Limited Prosocial Emotions, HC = healthy controls.

aforementioned effect sites does not relate to the LPE specifier total score, which indexes LPE severity, both within and across groups (*P's* > 0.05).

No sign of decreased neural activity was found in CD/LPE+ youth versus HC and CD/LPE- youngsters, nor did they exhibit altered neural responses in key affective regions such as the amygdala or insula, even when post-hoc region-of-interest analyses were performed. Finally, quadratic contrasts that treated CD/LPE+ and CD/LPE- youths as equals in comparison to HC youths, in search of CD commonalities, did not reveal any group effects within relevant cortico-paralimbic regions under scrutiny here. The only quadratic effect that did emerge was mainly diminished activity in the visual cortex in both CD groups relative to HC participants (Table S3), though this is not further elaborated on in the discussion, as the location and direction of this effect was not a-priori hypothesized (see Supplement for more detail).

4.4. Reaffirming LPE-specific neural signature

To assess whether the LPE is capturing a specific neural signal, we supplementary reran the fMRI analyses, in which similar to most prior work (e.g., Hwang et al., 2016; Sebastian et al., 2014; Viding et al., 2012), CD youths were now divided into high and low CU traits groups, based on a median split of the YPI-CU scale total scores, instead of the DSM-5 informed LPE specifier (see Supplement for details). Although CD youths with above-median CU levels partly exhibited the same pattern of frontoparietal hyperactivity during emotion recognition and resonance as CD/LPE+ youths did, the patterns were less pronounced (only visible at lenient thresholds: $P < 0.001$, uncorrected), more diffuse in nature, and importantly excluded medial frontal regions (Fig. S1). Further analysis revealed that this difference in outcome was mainly due to the LPE-based grouping producing a more extreme group of CD youths with high CU, than the median split grouping (see Supplementary Table S3 & S4). The analyses thus reveal that the LPE as specified here seems to capture a specific neural signal, when compared

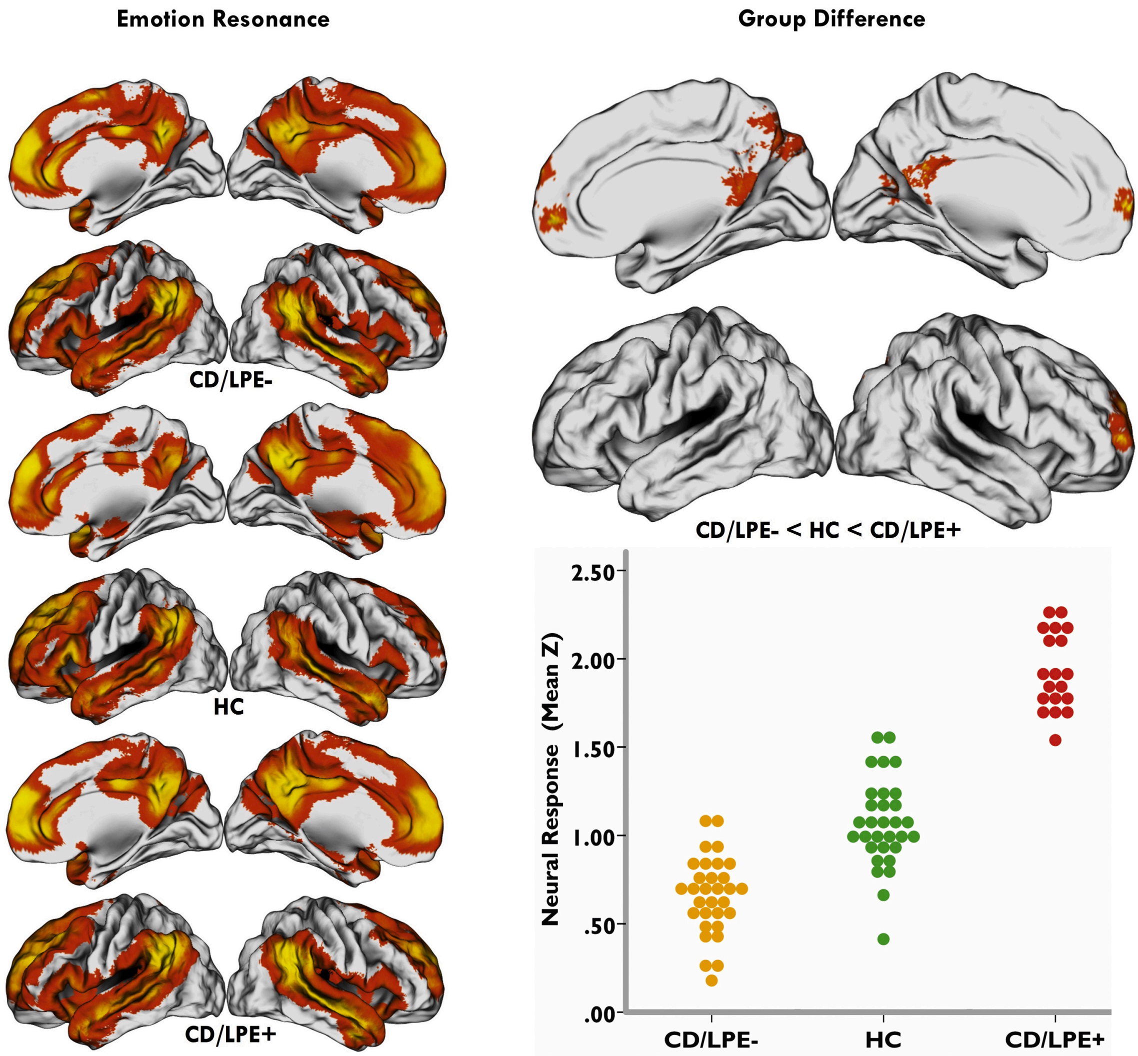

Fig. 4. Cortical hyperactivity during emotion resonance in CD/LPE+. The left panel depicts medial and lateral views of brain regions activated during emotion resonance in CD/LPE- (upper row), HC (middle row), and CD/LPE+ (lower row) participants. Relative to HC and CD/LPE- youths and according to a linearly increasing trend (CD/LPE- < HC < CD/LPE+), CD/LPE+ youth exhibited hyperactivity within a network including lateral and medial portions of the prefrontal cortex, along with posterior cingulate and precuneal cortices (right panel upper row). The distribution plot (right panel lower row) provides a quantitative visualization of this linear effect, wherein neural response estimates (y axis) as indexed by z-values averaged across all illuminated voxels are plotted for each group (x axis). FSL's FEATquery tool was used to extract these subject-level neural response estimates (i.e., mean Z-values) within depicted brain clusters showing the linear group effect. All statistical maps are non-parametrically thresholded and family-wise error corrected (threshold $Z > 2.3$, significance $P < 0.01$). CD/LPE+ = conduct disorder with Limited Prosocial Emotions; CD/LPE- = conduct disorder without Limited Prosocial Emotions, HC = healthy controls.

to a commonly employed method for CU-based grouping in CD (i.e., median split on CU scores).

5. Discussion

Little is known of how CU traits as categorically defined by the DSM-5 LPE specifier may impact socioemotional neural processing in CD youths. Employing a DSM-5 informed LPE proxy, neural processing of recognizing and resonating negative socioemotional content (angry and fearful faces) was therefore examined here in juvenile offenders with CD/LPE+ and CD/LPE-, as well as HC youngsters. Largely in line with our hypotheses, we found evidence for disorder-specific hyperactivity within regulatory cortical circuits among CD/LPE+ youth, when recognizing or resonating negative socioemotional content. This might suggest an over-reliance on cortical neurocognitive systems in CD/LPE+ youth when explicitly processing negative socioemotional content, which could have adverse downstream effects on relevant socioemotional functions. These findings provide novel, yet preliminary, clues on CD/LPE+ neurocognitive profile, and additionally highlight the potential scientific utility of the LPE specifier.

5.1. Frontoparietal hyperactivity in CD/LPE+ during effortful socioemotional processing

Relative to HC and CD/LPE- youths and according to a linearly increasing trend (CD/LPE- < HC < CD/LPE+), CD/LPE+ youth exhibited hyperactivity within dorsolateral, dorsomedial, and ventromedial prefrontal regions during both emotion recognition and resonance. The prefrontal cortex is a highly evolved cortical region, comprised of functionally specialized subregions that contribute differentially to cognitive control of attention, emotion, and action. For instance, while dorsolateral regions seem to support top-down attentional control and higher order executive processes, dorsomedial and ventromedial sections are deemed crucial in response selection and cognitive control of emotion (Arnsten and Rubia, 2012). Our results, therefore, may cautiously suggest that CD/LPE+ is characterized by an over-reliance on cognitive deliberation when explicitly dealing with negative affective stimuli, a feature increasingly documented in (young)adults with psychopathic tendencies as well (Anderson et al., 2017; Contreras-Rodriguez et al., 2014; Decety et al., 2013a; Decety et al., 2015; Decety et al., 2014; Decety et al., 2013b; Sadeh et al., 2013; Yoder et al., 2015a; Zijlmans et al., 2018). In fact, prefrontal hyperactivity during explicit emotion processing among psychopathic individuals is surmised to reflect an over-reliance on cognitive (controlled) computations, in order to compensate for intrinsic affective deficits (Contreras-Rodriguez et al., 2014; Decety et al., 2013a; Decety et al., 2015; Decety et al., 2014; Decety et al., 2013b; Sadeh et al., 2013; Yoder et al., 2015a).

Along these lines, we thus tentatively speculate that CD/LPE+ youth may recruit compensatory cortical resources to accomplish explicit emotion recognition and resonance, which could partly explicate their relatively preserved task performance in the current investigation. Following this perspective, both adults and adolescents with psychopathic traits have indeed been shown capable of performing rather well on tasks requiring explicit processing of socioemotional information, speculatively by recruiting compensatory cortical operations (Alegria et al., 2016; Contreras-Rodriguez et al., 2014; Decety et al., 2015; Zijlmans et al., 2018). It should be noted, however, that during *more implicit* emotion processing (e.g., passive viewing/gender discrimination/moral dilemmas) cortical and subcortical circuits commonly exhibit *hypoactivity* in both adults and adolescents with psychopathic tendencies (Anderson and Kiehl, 2012; Blair et al., 2014; Blair, 2013b; Harenski et al., 2014; Harenski et al., 2010; Pujol et al., 2012), consonant with context-dependent influence of psychopathic traits on neurobehavioral functions (Decety et al., 2015; Hamilton et al., 2015). We thus tentatively theorize that neurofunctional alterations reported here are specific to *explicit* processing of negative socioemotional content in CD/LPE+ patients. Hence, future work should aim to reveal whether neurobehavioral underpinnings of implicit emotion processing are similarly impacted in this clinically relevant population.

Our results further revealed that during emotion resonance, CD/LPE+ youth also showed higher activity than HC and CD/LPE- youths, respectively (CD/LPE- < HC < CD/LPE+), within the posterior cingulate and precuneal cortices, regions potentially relevant to psychopathic traits (Anderson and Kiehl, 2012; Decety et al., 2013a; Juarez et al., 2013; Yoder et al., 2015b). While these neighboring cortical structures clearly serve myriad of functions, they are increasingly recognized as key nodes within the so-called mentalizing network, whose network function putatively supports internally and externally directed socioaffective processes (Andrews-Hanna et al., 2010; Barrett and Satpute, 2013; Bickart et al., 2014; Li et al., 2014). Noteworthy, the hyperactive medial prefrontal territories mentioned earlier in CD/LPE+ youth during emotion resonance, are also deemed integral components of this network constellation (Andrews-Hanna et al., 2010; Barrett and Satpute, 2013; Bickart et al., 2014; Li et al., 2014). Within this putative circuitry, the posterior cingulate, precuneal, and medial prefrontal cortices seem to accommodate self-other dichotomies, self-relevant evaluative processes, and emotional engagement during social interactions, along with dynamic inferences about others' socioaffective state (Andrews-Hanna et al., 2010; Barrett and Satpute, 2013; Bickart et al., 2014; Li et al., 2014).

Altered functional integrity of such a system as documented here, may thus speculatively bias flexible reallocation of cognitive resources between internally and externally directed socioaffective processes, plausibly impeding the visceroaffective sensation necessary for interpersonal emotion resonance. Anomalies in these processes have been suggested in relation to CU traits (Bird and Viding, 2014; Blair, 2013a; Frick and Viding, 2009), and tentatively ascribed to perturbations within the mentalizing network discussed here (Decety et al., 2015; Juarez et al., 2013; Philippi et al., 2015). It is noteworthy that the only MRI study to date comprising CD/LPE+ youth based on DSM-5 criteria, additionally reveals perturbed structural connectivity between key nodes of this mentalizing system (Sethi et al., 2018b). Intriguingly though, it is also hypothesized that while some *overt* socioemotional behaviors might seem ostensibly preserved in individuals with psychopathic traits (as documented here), their socioemotional repertoire is essentially shallow and callous due to atypical neurovisceral processing of emotions (Bird and Viding, 2014; Marsh et al., 2008; Yoder et al., 2015a). Along these lines, we thus cautiously link CD/LPE+ to a neurobiological profile prone to incite inflexibilities within the socioemotional domain, and shape social interactions that are self-centered and emotionally callous. Future studies are warranted, though, to further explore and validate our interpretation, given the complexity of socioemotional brain systems and their modulation of actual socioemotional behavior, in both healthy and clinically antisocial populations.

5.2. Opposing frontoparietal reactivity in CD/LPE+ vs. CD/LPE-

In line with our hypotheses, CD/LPE+ and CD/LPE- youths showed opposing frontoparietal neural responses, when recognizing or resonating emotions. As mentioned in the introduction, these opposing neural responses coincide with the qualitatively disparate emotion processing deficits commonly found in these two heterogenous CD populations. Whereas preserved cognitive-emotional understanding and lack of affective contagion/resonance is typical to CD/LPE+ youth, their CD/LPE- peers seem more susceptible to emotional dysregulation and associated impediments in cognitive understanding of others' emotions (Blair et al., 2014; Blair, 2013a; Fairchild et al., 2019). Differential cortico-paralimbic reactivity to negative emotions/valence seems to underpin these divergent behavioral effects, wherein CD/LPE+ youth conjointly exhibit *(para)limbic hyporesponsivity* and *excessive cortical recruitment*, while the CD/LPE- youth show the opposite neural pattern (Blair et al., 2014; Blair, 2013a; Fairchild et al., 2019).

Though we did not find any group differences in (para)limbic function (amygdala/insula/striatum), the allegedly opposing cortical regulatory responses were reaffirmed here, as evidenced in the group-specific frontoparietal reactivity patterns (CD/LPE+ = excessive & CD/LPE- = insufficient). The exact mechanisms behind these ostensibly differential neural patterns remain largely unknown, though subtle variations in the (epi)genetic and molecular landscape have been tentatively implicated (Blair et al., 2014; Blair, 2013a; Fairchild et al., 2019; Gard et al., 2019). In fact, using the same fMRI-task, we recently showed that elevated CU traits in CD youth interact with *OXTR* epigenetic methylation levels to predict frontoparietal hyperactivity, when recognizing/resonating negative emotions (Aghajani et al., 2018). Future studies are clearly needed to dig deeper into mechanisms that may propel the differential neurobehavioral profiles of CD/LPE+ vs. CD/LPE-, which could ultimately aid tailored treatment strategies for these two CD populations.

5.3. Task-related amygdalar/insular reactivity unaffected in CD/LPE+

Interestingly, CD/LPE+ youth did not exhibit altered neural processing of socioemotional content in key affective regions such as the amygdala or insula, thus contrasting some of the previous work among antisocial youth with CU traits (Blair et al., 2014; Blair, 2013a). It is good to first highlight how the field is increasingly acknowledging that the link between amygdalar or insular activity and CU traits is more complex and subtle than previously appreciated. For instance, a recent study found that juvenile CU traits don't affect amygdalar activity, but instead relate to increased (rather than decreased) insular responses, during a task also involving recognition and resonance of socioemotional content (Gao et al., 2019). Such findings further echo the complexity of CU traits and their neurobehavioral underpinnings, warranting further exploration of previously documented brain-behavior relationships.

In addition, prior work has commonly shown diminished amygdalar or insular responses to distress cues relative to *neutral cues* among high CU youths (e.g., Blair, 2013a; Viding et al., 2012; White et al., 2012), whereas we contrasted distressing emotion conditions to high-level control conditions (decision on width of faces). This methodological difference may in part account for the lack of amygdalar/insular effects in the current study. A good portion of prior studies on the topic moreover failed to include a comparison group of antisocial youths *without* CU traits, and may have therefore demarcated a neural response seen in juvenile antisocial populations in general, rather than antisocial youths *with* CU traits in particular. Additionally, and perhaps more relevantly, while explicit emotion manipulation was utilized in this study, prior work on the topic typically employed more implicit/indirect emotion processing paradigms (e.g., passive viewing, moral dilemmas, gender discrimination) (Blair et al., 2014; Blair, 2013a), which may conceivably account for some of the discrepancies between current and previous findings. Previous work among psychopathic individuals additionally suggests that explicit instructions to focus on negative emotional stimuli could ameliorate limbic dysfunction by increasing top-down attentional processes, ostensibly mediated by medial and lateral prefrontal territories (Anderson et al., 2017; Larson et al., 2013). Given the explicit nature of our task and the elevated activity of these prefrontal regions in CD/LPE+ participants, this may also partly explicate the lack of amygdalar/insular effects in the current study, a notion that resonates well with recent work on psychopathy (Decety et al., 2014).

5.4. Study limitations and strengths

The scanner environment only allows examination of proxies for complex social and emotional processes, and therefore, precludes firm conclusions regarding neural processes that might be at play during real-life socioemotional encounters, a limitation inherent to practically all task-fMRI studies. The limited age range (15–19 years) and modest size of our sample additionally preclude thorough examination of any developmental/age-related effects on neurofunctional changes documented here. The small sample of CD/LPE+ youth is especially unfortunate and potentially detrimental for picking up subtle effects. That said, neurobiological research within forensic setting typically suffers from small sample sizes, with our sample therefore being comparable to (in some cases even bigger than) majority of prior work on the topic (e.g., Blair, 2013a; Sethi et al., 2018a; Sethi et al., 2018b; White et al., 2012). Future studies among larger samples with wider age ranges, and preferably longitudinal in nature, are warranted to address these issues directly. Further, we lacked reliable data on long-term substance use among our participants (we only had data on past month use), while logistic and legal issues prevented biological testing of substance use prior to the scanning session. As such, we are unable to fully tease out the potential impact of substance use on neural alterations reported here. We also lacked diagnostic data on mood/anxiety disorders, as time constraints and increased participant burden hindered clinical diagnostic assessment of these disorders. Our sensitivity analyses revealed, however, that correction for general internalizing symptomatology (depressive/anxious tendencies) does not affect the results documented here.

Lastly, the YPI questionnaire we used for establishing LPE allows an approximation of the LPE specifier as outlined in DSM-5, as is the case with most instruments that are currently used to establish LPE in CD youngsters. We also lacked multi-informant data (parents/care givers) on LPE criterions, as these were solely assessed based on YPI self-reports, which could affect the LPE classifications. The challenging forensic settings from which we recruited our CD youth greatly limited the possibility of parents/care givers involvement, with DSM-5 also not necessitating multi-informant data for establishing LPE (APA, 2013a). The YPI moreover does not directly assess the LPE specifier criterion "unconcerned about performance". Evidence nonetheless affirms the validity of the YPI in reliably assessing the LPE specifier, also when compared to other tools that are used to assess the LPE criteria (Colins and Andershed, 2015). Crucially, according to DSM-5, CD youths will fulfill the LPE specifier if they meet *at least two* of the four LPE criteria, rendering the YPI thus well suited to probe LPE in CD populations (for details see: Colins and Andershed, 2015; Colins and Vermeiren, 2013). It is imperative to note that the clinical and conceptual relevance of the criterion "unconcerned about performance" has been seriously questioned, mainly because of its insufficient discriminatory power and susceptibility to over-sampling (Colins, 2016; Lahey, 2014; Salekin, 2016). Our findings thus provide an interesting focus for future research into CD/LPE+, which not only should explore and validate the neural perturbations reported here, but also probe the potential impact of using different, yet closely related, classification schemes of CD/LPE+.

Notwithstanding these limitations, the current study also has several strengths that are worth mentioning. It is the first fMRI study in CD youth that examines the impact of CU traits, as categorically informed by the DSM-5 LPE specifier, on socioemotional processing and its putative neural circuitry. While prior work has been imperative in establishing a rationale for developing the LPE specifier, studies such as ours are urgently needed to directly evaluate its clinical/scientific utility and neurocognitive correlates. In addition, whereas CU traits have been extensively examined in relation to socioemotional processing in CD youths, a thorough and integrated understanding of CU-related effects is currently lacking, owing partly to discrepancies in CU operationalization (e.g., dimensional measure/median split/top quartile). The LPE specifier can provide researchers and clinicians with a standardized, easy to use, and widely accepted measure for identifying high-risk CD youths based on their CU levels, and this is anticipated to improve our understanding of underlying pathophysiology, and aid clinical care and prognosis (Frick et al., 2014; Kimonis et al., 2015). The LPE specifier, however, is by no means superior to the concept of CU traits as a whole, it merely provides a standardized means for establishing clinical levels of CU in CD youth. The LPE was in fact born out of the rich empirical work on CU traits, and the hypotheses and interpretations presented here are deeply rooted in that work.

On top of these issues, we also recruited a unique group of juvenile CD offenders that typically forfeit/decline enrollment in scientific studies, while additionally matching our groups on age and IQ, and correcting for key clinical and sociodemographic factors. The age range was additionally restricted to 15–19 years, and only medication-free participants were recruited to mitigate confounding effects of age distribution and medication on brain function.

6. Conclusions

In summary, the current findings provide tentative evidence for disorder-specific hyperactivity within regulatory cortical circuits among CD/LPE+ youngsters, when recognizing or resonating negative socioemotional content. This might suggest an over-reliance on cortical neurocognitive systems in CD/LPE+ youth when explicitly processing negative socioemotional content, which could have adverse downstream effects on relevant socioemotional functions. These findings provide novel, yet preliminary, clues on the neurocognitive profile of CD/LPE+, and highlight the potential scientific utility of the LPE specifier, which should be further explored and validated in the future.

Author contributors

Moji Aghajani and Olivier Colins contributed to the conceptualization, design, methodology, and data analysis of this paper. All authors contributed to the writing of the paper.

Ethical statement

Our study was conducted in accordance with the declaration of Helsinki and approved by the medical ethics committee of the Leiden

University Medical Center. We declare that written informed consent was obtained from all participants. The authors furthermore declare no conflict of interest.

Financial disclosure

The authors report no biomedical financial interests.

Declaration of Competing Interest

The authors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2020.110045.

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