Investigating Sex Differences in Emotion Recognition, Learning, and Regulation among Youths with Conduct Disorder

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Acknowledgements: This study was funded by the European Commission's Seventh Framework Programme (FP7/2007-2013) under Grant Agreement no.602407 (FemNAT-CD, coordinator: Christine M. Freitag).

Presentations information: Preliminary data were presented at the European Society for Child and Adolescent Psychiatry, Madrid, Spain (2015) and Geneva, Switzerland (2017); the European Association for Forensic Child and Adolescent Psychiatry, Porto, Portugal (2016); and the 72nd Annual Meeting of the Society of Biological Psychiatry, San Diego, USA (2017).

Disclosures: Prof. Konrad has received speaker fees from Shire Pharmaceuticals and Medice. Prof. Stadler receives royalties for a book on aggression. Prof. Freitag receives royalties for books on ADHD, ASD, and Depression. She has served as consultant to Desitin and Roche. Prof. Dikeos received speakers fees and served as consultant to Angelini, AstraZeneca, Boehringer, Bristol Myers Squibb, Eli Lilly, Genesis Pharma, GlaxoSmithKline, Janssen, Lundbeck, Organon, Sanofi, Servier, UniPharma, and Wyeth. Dr. De Brito has received speaker fees from the Child Mental Health Centre and the Centre for Integrated Molecular Brain Imaging. All other authors report no biomedical financial interests or potential conflicts of interest.

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Running head: Emotion deficits in CD girls versus boys

Word count (without abstracts, tables, figures, or references): 4637

Keywords: Conduct disorder, emotion processing, sex differences, callous-unemotional traits, FemNAT-CD

Abstract

Objective: Conduct disorder (CD) is a serious neurodevelopmental disorder marked by notable higher prevalence rates for males than females. Converging evidence suggests that CD is associated with impairments in emotion recognition, learning and regulation. However, it is not known whether there are sex differences in the relationship between CD and emotion dysfunction. Prior studies on emotion functioning in CD have so far been underpowered for investigating sex differences. Therefore, our primary aim was to characterize emotion processing skills in a large sample of females and males with CD compared to typically-developing controls (TDCs) using a comprehensive neuropsychological test battery.

Method: We included 542 youths with CD (317 females) and 710 TDCs (479 females), aged 9-18 years, from a European multisite study (FemNAT-CD). Participants completed three experimental tasks assessing emotion recognition, learning, and regulation, respectively. Data were analyzed to test for effects of group and sex, and group-by-sex interactions, while controlling for potentially confounding factors.

Results: Relative to TDCs, youths with CD showed impaired emotion recognition (that was related to more physical and proactive aggression, and higher CU traits), emotional learning (specifically from punishment), and emotion regulation. Males and females with CD, however, displayed similar impairments in emotion processing.

Conclusion: This study provides compelling evidence for a relationship between CD and deficient neurocognitive functioning across three emotional domains that have previously been linked to CD etiology. However, there was no support for sex-specific profiles of emotion dysfunction, suggesting that current neurocognitive models of CD apply equally to both sexes.

Introduction

Conduct disorder (CD) is a psychiatric disorder involving severe antisocial and aggressive behaviors that emerge in childhood or adolescence[1]. It places a substantial burden on the affected individuals, their families and carers, and incurs enormous healthcare and societal costs[2]. Youths with CD, however, are a markedly heterogeneous group in terms of clinical presentation, psychosocial outcome, and contributing risk factors[3]. Despite considerable investigation and speculation, the neurocognitive mechanisms that contribute to CD remain incompletely understood. In fact, several neurocognitive domains have been described that may contribute to the risk of developing disruptive behavior[4], including lower-than-average intelligence, language disorders, deficient executive functioning (e.g., response inhibition and working memory problems), and aberrant social cognitive and emotion processing skills[5]. Because deficits vary greatly in manifestation and severity among CD individuals, it has been suggested that different neurocognitive domains may be associated with different pathways, and expressions of CD behaviors, including aggression[4]. Recent theoretical models emphasizing emotion dysfunction have been particularly influential in this regard[6–9]: For example, it has been proposed that diminished responsiveness to distress cues, such as fearful facial expressions, is specifically linked to CD with callous-unemotional (CU) traits (i.e., lack of guilt and empathy, callousness, and uncaring attitudes), accounting for a particularly severe, early-starting and chronic trajectory of antisocial behavior, including proactive aggression. In contrast, CD youths without these traits typically show problems regulating their emotional impulses reflected in heightened reactivity to negative emotional stimuli which may result in reactive aggressive acts[7–9].

Although CD is less prevalent and often emerges later in girls than in boys, it is still one of the most common psychiatric disorders leading to referral to mental health services in female youths[10]. Nevertheless, the study of CD problems and their underlying neurocognitive mechanisms has traditionally focused primarily on males. Thus, there is an urgent need to

understand whether the proposed neurocognitive models of CD can be generalized to females[11], or whether different, more female-tailored accounts are required to explain the origins of antisocial behaviors in girls[12].

Research suggests that emotion processing skills may provide a particularly powerful framework for explaining potential sex differences in CD[13]. Typically, females outperform males on social cognitive, including emotion processing, tasks[14]. This female advantage emerges early in development, continues through childhood and adolescence, and may derive from earlier maturation of brain systems involved in emotional responsivity and regulation[15]. As girls display greater emotion functioning skills than boys, they appear to be better equipped for the challenges of socialization[13]. Traditional gender roles also encourage more prosocial behavior in girls[16]. Thus, for female CD to emerge, girls may require a greater liability, i.e., more severe constellation of risk factors, in order to develop serious antisocial behaviors in line with the *differential threshold hypothesis* of female CD[17] (but see[11]). Thus, one might speculate that girls with CD would show greater emotion dysfunction relative to typical females than CD boys[13].

To date, studies on emotion functioning in CD have been unsuited or underpowered for testing for sex-by-group interactions as they primarily focused on predominantly male or female samples. Prior work has been further limited by relying on relatively small samples with varying selection criteria and neuropsychological tasks[18], including mixed samples of youths with CD or oppositional defiant disorder (ODD), or focusing on a single subdomain of emotion dysfunction. However, it has recently been hypothesized that three domains of emotion dysfunction are causally related to CD, including emotion recognition, learning, and regulation[4,8,9]. To date, these domains have not been comprehensively investigated in the same sample to directly compare patterns of dysfunction in girls and boys with CD relative to sex-matched typical youths. Thus, to address the above-mentioned research gaps, we applied

a comprehensive neurocognitive test battery that covers all three emotion domains in the context of a large-scale multisite study[19].

Because youths with CD often show difficulties in perceiving other peoples' emotions[20], we first assessed the ability to identify facial expressions depicting the six basic emotions using the Emotion Hexagon task[21]. Prior male- and female-only studies using this task revealed impaired recognition of anger and disgust in CD in both sexes[22,23], and a relatively selective deficit in perceiving fearful and sad expressions in the CD subgroup with psychopathic traits[22,23]. Second, deficits in emotional learning were tested with the Passive Avoidance Learning task[24] as reduced emotional learning has been demonstrated across various subgroups with conduct problems, including CD youths with or without CU or psychopathic traits, and youths with ODD or attention-deficit/hyperactivity disorder (ADHD)[8]. In this task individuals with CD show no impairment in responding to stimuli predicting reward, but are significantly more likely to fail to avoid responding to stimuli predicting punishment than typical individuals[18,25]. This learning style suggests difficulties in assigning punishment values to stimulus-reinforcement contingencies when competing rewards are present[26]. Two studies with adolescent samples suggested that deficits in passive avoidance learning may be specific to antisocial males, whereas antisocial females showed intact punishment-based learning[27,28]. Thirdly, we assessed emotion regulation and non-emotional cognitive control skills by administering the Emotional Go/Nogo task[29]. While emotion regulation deficits have been linked to reactive aggression in several externalizing disorders, including CD, ODD, and ADHD[30], cognitive control deficits have been associated with impulsive behaviors in these disorders[31].

Thus, we predicted that, compared to typically-developing controls (TDCs), both boys and girls with CD would show deficits in: (1) recognizing angry, fearful, sad, and disgusted facial expressions[22,23]; (2) punishment-based learning (though prior evidence also suggested that this deficit might be male-specific[27,28]); and (3) inhibiting behavioral responses in the

context of interfering emotional stimuli. On the basis of the *differential threshold hypothesis* of female CD[17], we further hypothesized that females with CD would show more pronounced emotion dysfunction relative to typical girls than CD boys (vs. typical boys). We further addressed the *delayed-onset pathway hypothesis* of female CD[12]: As the onset of CD is usually delayed until adolescence in females (i.e., it manifests as adolescent-onset CD; AO-CD), despite common risk factors with childhood-onset CD (CO-CD) males[11], this hypothesis suggests that AO-CD females would show neurocognitive deficits similar to CO-CD males, with AO-CD males being the least impaired group. Thus, we also tested for sex-by-age-of-onset interaction effects on our dependent measures of emotion functioning. We additionally predicted associations between: (1) emotion recognition deficits and CU traits; (2) emotion dysregulation and reactive aggression; and (3) cognitive control deficits and impulsive symptoms in CD youths[32].

Method

Participants

This study included 542 youths with CD (317 females) and 710 TDCs (479 females), aged 9-18 years, from the European "Neurobiology and Treatment of Female Conduct Disorder" (FemNAT-CD) project[19]. Girls were oversampled as one of the main aims of the overarching study was to address the lack of data on females with CD. We included participants who provided a complete neuropsychological dataset, comprising the Emotion Hexagon task, the Passive Avoidance Learning task, and the Emotional Go/Nogo task (see below). Participants were recruited through community outreach as well as from mental health clinics, welfare institutions, and youth offending services. Overall exclusion criteria were IQ<70, autism spectrum disorders, schizophrenia, bipolar disorder or mania, neurological disorders, and genetic syndromes. Youths with CD had a current CD diagnosis according to DSM-IV-TR criteria[33]. Participants who were taking psychotropic medication (30.2% of all CD cases) were

tested while on medication (Table S2, available online). TDCs were free of current DSM-IV-TR diagnoses, and had no history of CD, ODD, or ADHD. Local ethics committees at each site approved the study protocol. Written informed consent was obtained for all participants.

Youths with CD and TDCs were assessed with the Kiddie-Schedule for Affective Disorders and Schizophrenia–Present and Lifetime version (K-SADS-PL[34]), administered separately to participants and their caregivers by trained staff members to assess psychiatric diagnoses. Inter-rater reliability (IRR; n=75, i.e., n=5-8 per site) of CD was high (Cohen's κ=0.91), with an agreement rate of 94.7%. IRR of other disorders, including ADHD, ODD, major depressive disorder (MDD), and generalized anxiety disorder (GAD), was also high (Cohen's κs≥0.84, agreement rates ≥92%). Disorder severity was defined as the number of symptoms endorsed in the K-SADS-PL interviews. Using the K-SADS-PL, we also determined (a) severity for the four symptom domains of CD (i.e., physical aggression, destruction of property, deceitfulness/theft, and rule violation), and (b) CD-onset type (i.e., CO-CD: presence of at least one characteristic CD behavior prior to age 10; AO-CD: absence of any CD behaviors prior to age 10)[1]. Full-scale IQs were estimated using the vocabulary and matrix reasoning subtests of the Wechsler Intelligence Scale for Children-Fourth Edition[35], or the Wechsler Adult Intelligence Scale-Fourth Edition[36]; English sites used the Wechsler Abbreviated Scale of Intelligence[37]. CU traits scores were derived from the self-report Youth Psychopathic traits Inventory (YPI) (i.e., total score for the subscales "remorselessness", "unemotionality", and "callousness"; Cronbach's α=0.81)[38]. Participants reported on their own aggressive behaviors using the Reactive-Proactive aggression Questionnaire (RPQ; Cronbach's α=0.90)[39], and the Relational Aggression Questionnaire (RAQ; Cronbach's α=0.86)[40].

Neuropsychological test battery

Briefly, we used the Emotion Hexagon task to assess the accuracy (in %) of facial emotion recognition[21], including happy, sad, angry, fearful, disgusted, and surprised expressions. We used a modified Passive Avoidance Learning task to assess emotional learning[24], such that participants had to learn by trial-and-error to respond to stimuli eliciting rewards (winning points) and to avoid responding to stimuli eliciting punishments (losing points). Responses to punishment stimuli were counted as passive avoidance (commission) errors, and non-responses to reward stimuli were counted as omission errors. Finally, we administered the Emotional Go/Nogo task to assess the accuracy of emotion regulation, defined as the ability to maintain cognitive control when confronted with interfering emotional stimuli, including negative facial expressions[29]. Participants were instructed to press a response button as quickly and accurately as possible whenever a named facial expression appeared on the screen (go trials) and not to press for any other expression (no-go trials). We considered false alarm rates (i.e., commission errors in %) specifically to emotional nogo stimuli (e.g., happy, fearful) in the context of neutral go stimuli (i.e., neutral expressions) as our index of emotion regulation. The rate of commission errors to neutral nogo stimuli was our index of non-emotional cognitive control. Lower numbers of commission errors reflected better performance. Order of tasks was pseudorandomized separately for group (CD, TDC), sex (female, male), and age brackets (9-12, 13-15, 16-18 yrs.). More details on the test battery and procedure can be found in Figure 1 and in the Supplement (available online).

[Figure1]

Statistical analyses

We compared groups on demographic and clinical variables with analyses of variance (ANOVA) and Chi-Square tests (SPSS v25, IBM Corp., Armonk, NY). We analyzed the dependent measures of emotion functioning separately for the three neuropsychological tasks, using three repeated-measures analyses of covariance (rmANCOVA) with group (CD vs.

TDC, and CO-CD vs. AO-CD) and sex (female vs. male) as between-subject factors and condition as the within-subject factor, followed by post-hoc pairwise comparisons in case of significant main or interaction effects. Alpha levels of these post-hoc comparisons were adjusted using Bonferroni corrections to control for multiple comparisons separately within each experimental paradigm. Because age and IQ differed significantly between groups and were correlated with the neuropsychological variables (rs≥0.07, ps≤.05), they were entered as covariates in all models, including the correlational analyses. Site was entered as a random variable of no interest. In addition, each rmANCOVA was repeated including psychotropic medication status (0=no, 1=yes) as well as comorbid diagnoses of ADHD (as categorical and dimensional variable), MDD, GAD, post-traumatic stress disorder (PTSD), and substance use disorder (SUD) as covariates of no interest. Effect sizes were calculated using partial eta squared (η^2_p), where 0.01, 0.06, and 0.14 represent small, medium and large effects, respectively[41]. Our sample size was large enough to detect even small effects, including sex-by-group interaction effects, with a power of 80% and a two-sided significance level of 5% (G-Power 3.1), on each neuropsychological task. Although several variables were not normally distributed, all data were analyzed with parametric tests as the sample size was sufficiently large[42].

Results

Demographic characteristics

Table 1 summarizes the sample's main demographic and clinical characteristics. CD girls were older than the other groups, showed the highest relational aggression scores (RAQ) and had the most rule violations (K-SADS-PL). In contrast, CD boys showed the highest levels of physical aggression and destruction of property (K-SADS-PL). Across sexes, youths with CD had lower IQs, and reported higher reactive and proactive aggression (RPQ) than TDCs. The CD groups also displayed higher levels of CU traits (YPI) than their typical peers.

Interestingly, while male TDCs scored higher in CU traits than female TDCs, there were no significant sex differences in the CD group. Within the CD group, males presented more frequently with CO-CD than AO-CD, whereas females showed the opposite age-of-onset pattern. ADHD was more common among CD boys than girls, whereas CD girls showed more PTSD and borderline personality disorder (BPD) symptoms. Lastly, CD males reported higher psychotropic medication use for ADHD than females (Table S2, available online).

[Table1]

Emotion recognition: For the Hexagon task, the rmANCOVA revealed significant effects of condition [$F(3.6, 4374.4)=139.01$, $p<.001$, $\eta^2_p=0.10$], sex [$F(1, 1213)=10.01$, $p=.002$, $\eta^2_p=0.008$], and group [$F(1, 1213)=25.11$, $p<.001$, $\eta^2_p=0.02$], but no significant interactions between these factors, including no significant sex-by-group and sex-by-group-by-condition effects (ps>.096, η^2_ps≤0.002). Overall, accuracy was highest for happiness (1), followed by sadness (2) and surprise (3), and performance was poorest for fear (4), anger (5), and disgust (6): 1>2=3>4=5=6 (all significant pairwise ps$_{\text{Bonferroni-corrected}}$ <.001). Overall, females outperformed males (77.8%±0.6 vs. 73.3%±1.2), and CD youths were worse at recognizing facial expressions than TDCs (Figure 2A). Notably, the group-by-emotion interaction was non-significant ($p=.57$, $\eta^2_p=0.001$), indicating that the effect of CD was similar across positive and negative emotions.

Emotional learning: For the Avoidance task, the rmANCOVA revealed significant effects of condition [$F(1, 1213)=493.98$, $p<.001$, $\eta^2_p=0.29$], group [$F(1, 1213)=4.87$, $p=.028$, $\eta^2_p=0.004$] and sex [$F(1, 1213)=4.98$, $p=.026$, $\eta^2_p=0.004$], as well as a significant group-by-condition interaction [$F(1, 1213)=5.99$, $p=.015$, $\eta^2_p=0.005$]. All interactions with the factor sex were non-significant (ps>.29, η^2_ps≤0.001). Overall, participants made more passive avoidance errors than omission errors (22.7±0.3 vs. 8.7±0.3), and males slightly outperformed females

across conditions (15.4±0.3 vs. 16.0±0.1). Compared to TDCs, CD youths made significantly more avoidance errors in the learning-from-punishment condition (23.7±0.5 vs. 21.7±0.5; $p_{\text{Bonferroni-corrected}}$=.003, η^2_p=0.007), but the CD and TDC groups showed similar rates of omission errors in the learning-from-reward condition (8.4±0.4 vs. 9.1±0.4; p=.19, η^2_p=0.001; Figure 2B).

Emotion regulation: For false alarm (FA) rates in the Go/Nogo task, the rmANCOVA revealed significant effects of condition [F(1, 1213)=10.98, p=.001, η^2_p=0.009], sex [F(1, 1213)=7.08, p=.008, η^2_p=0.006], and group [F(1, 1213)=21.75, p<.001, η^2_p=0.018], but no interactions between these factors, including no group-by-condition or sex-by-group-by-condition interactions (ps>.095, η^2_ps≤0.002). FA rates were higher in the emotion regulation condition (i.e., for emotional nogo stimuli: 38.3%±0.8) than in the non-emotional cognitive control condition (i.e., for neutral nogo stimuli: 35.4%±0.8). Females outperformed males (34.6%±0.7 vs. 39.5%±1.4), and CD cases overall had higher FA rates than TDCs (Figure 2C).

Taken together, these findings provide no support for the *differential threshold hypothesis* whereby girls with CD would show more pronounced emotion dysfunction relative to typical girls than CD boys.

[Figure2]

Testing the *delayed-onset pathway hypothesis* of female CD

To test predictions derived from the *delayed-onset pathway hypothesis* of female CD, we re-ran each rmANCOVA with CD-onset type (CO-CD vs. AO-CD) and sex (female vs. male) as the between-subject factors, but found neither significant age-of-onset effects nor interactions between sex and age-of-onset for any measure of emotion recognition (ps ≥ .13, η^2_ps ≤ 0.005) or emotional learning (ps ≥ .14, η^2_ps ≤0.001). However, there was a significant age-of-onset

effect on FA rates in the Go/Nogo task indexing emotion regulation (vs. non-emotion cognitive control), [$F(1, 483)=6.82$, $p=.009$, $\eta^2_p=0.014$], with the CO-CD group performing worse than the AO-CD group across conditions (44.8±2.0 vs. 38.8%±1.4); the sex-by-age-of-onset and the sex-by-age-of-onset-by-condition effects were non-significant (ps≥.08, η^2_ps≤0.006).

Correlations with CU traits, aggression, and impulsivity

Across the entire CD sample, we found weak, albeit significant, negative associations of overall emotion recognition performance with physical aggression (K-SADS-PL aggressive CD symptom count: $r_{partial}$=-0.13, $p_{Bonferroni\text{-}corrected}$=.004), CU traits ($r_{partial}$=-0.13, $p_{Bonferroni\text{-}corrected}$=.002), and proactive aggression (RPQ subscale: $r_{partial}$=-0.13, $p_{Bonferroni\text{-}corrected}$=.004), indicating that deficits in emotion recognition were related to more physical aggression symptoms, higher CU traits, and elevated proactive aggression in CD youths. Note: Although self-reported and parent-reported CU traits were significantly positively correlated ($r_{partial}$=0.37, p<.001), parent-reported CU traits were not significantly related to emotion recognition skills in CD ($r_{partial}$=-0.07, p=.13). Contrary to predictions, emotion dysregulation did not correlate significantly with reactive aggression (RPQ subscale: $r_{partial}$=0.002, p=.96), and cognitive control deficits did not correlate with impulsive symptoms (K-SADS-PL ADHD hyperactivity/impulsivity symptom count: $r_{partial}$=0.07, p=.09).

Controlling for potential confounders

All main and interaction effects for the factor group (CD vs. TDC) reported above remained significant after controlling for psychotropic medication use, and current comorbid disorders (ADHD, MDD, GAD, PTSD, and SUD). No novel sex-by-group or sex-by-group-by-condition effects emerged when including these covariates (Table S3, available online).

Discussion

To our knowledge, this is the first and the largest study to date to comprehensively investigate sex differences in three domains of emotion function linked to CD using a broad neuropsychological test battery within a single sample of CD youths compared to TDCs. Our results replicate and considerably extend prior findings from smaller-scale studies with predominantly male or female samples by demonstrating deficient facial emotion recognition (that was related to more physical and proactive aggression, and higher CU traits), poor emotional learning (specifically from punishment), and diminished emotion regulation that was accompanied by non-emotional cognitive control deficits in CD youths. As predicted, emotion deficits spanned across the three neurocognitive domains, but did not significantly differ between CD girls and boys. Within the context of influential notions about sex differences in CD, our data do not support the *differential threshold hypothesis* or the *delayed-onset pathway hypothesis* of female CD. The present findings challenge notions that females with CD show more pervasive neurocognitive deficits than males with CD and that there are sex-specific neurocognitive profiles in CD youths. Our data indicate that CD girls displayed similar profiles and degrees of emotion dysfunction as CD boys. Moreover, the four CD age-of-onset groups (i.e., CO-CD_f, CO-CD_m, AO-CD_f, and AO-CD_m) showed equivalent neurocognitive deficits, including the AO-CD boys who were equally impaired as the other three groups. Since our CD sample was representative compared to prior epidemiological studies (e.g.,[43]), including lower IQ than TDCs, accompanied by less CO-CD, ADHD and physical aggression, but more PTSD, BPD, and relational aggression in CD girls than CD boys[33] – we believe that the present findings can be generalized to the CD population at large. However, we acknowledge that using retrospective reports of disorder onset and severity as well as self-report measures of CU traits and aggressive behavior might limit our conclusions.

Our task-specific predictions were only partially confirmed: First, emotion recognition deficits in CD were not selective for specific emotions, such as sadness or fear, but more

pervasive across all six basic emotions. Also, elevated CU traits within the CD group were associated with overall emotion recognition impairments rather than deficits in particular emotions (esp. those conveying distress). While these findings are partly at odds with smaller-scale studies using the Hexagon task in separate samples of CD boys[23] and girls[22] reporting deficits that were specific for certain emotions depending on CD (e.g., anger) and CU traits status (e.g., sadness), they are in line with the latest meta-analysis on this topic[20]. Second, CD youths displayed the expected pattern of deficient learning from punishment but intact reward-based learning. The hypothesized male-specific impairments reported previously[27] did not emerge. Consistent with our findings, Fairchild and colleagues observed deficient aversive conditioning – an objective measure of emotional learning – among both females[22] and males[44] with CD, regardless of CU traits. Third, as predicted for our measure of emotion regulation, both CD girls and boys showed difficulties in inhibiting impulsive responses in the presence of emotionally interfering stimuli, consistent with prior findings[45]. This was accompanied by cognitive control deficits. Unexpectedly, emotion dysregulation was unrelated to reactive aggression, and cognitive control deficits were unrelated to impulsive symptoms in CD youths. Other aspects of emotion regulation, including the capacity to reappraise emotionally-arousing stimuli, and how this interacts with cognitive control mechanisms, are worth investigating in future studies.

Our study had several strengths: We tested a large, representative sample of females and males with and without CD that even included a sizable number of girls with the relatively rare form of CO-CD (N=100). To enable clear interpretation, we did not include a mixed clinical group of participants with CD or ODD as it is still premature to conclude that the same neurocognitive mechanisms underlie the etiology of both disorders[46] (but see[4]). The entire sample was comprehensively clinically assessed and reliably diagnosed using standardized, semi-structured interviews based on DSM-IV criteria that enabled us to account statistically for common psychiatric comorbidities as potential confounding factors. Finally,

we applied a comprehensive neurocognitive test battery that bridged different core emotion domains related to CD, allowing us to evaluate multiple emotion processing abilities simultaneously within the same sample.

However, this study also had several limitations: Individuals were recruited from various European sites, each contributing different sample sizes and uneven sex distributions (Table S1, available online). To reduce the impact of this factor, site was included as covariate in all analyses. Second, the sample ranged in age from 9-18 years, and groups differed in mean age and IQ. As age and IQ are known to influence neuropsychological performance throughout development[47], we included both as additional covariates in our analytic models. Third, we excluded TDCs with lifetime histories of and/or current disruptive behavior disorders, such as ADHD, ODD, and CD, in order to rule out the influence of any subclinical or precursor symptoms that are potentially linked to CD. However, this approach likely created a "super-normal" control group which is less representative of the general population in rates of psychiatric symptoms[48]. Fourth, the cross-sectional study design precludes us from inferring whether emotion deficits are, at least partially, causally related to the emergence of CD or a consequence of the disorder. This highlights the need for prospective longitudinal data from younger, at-risk children to determine if different aspects of emotion dysfunction are stable across development and how they contribute to pathways of antisocial behaviors. Finally, it should be noted that the effect sizes for the case-control differences in task performance were relatively small. This most likely reflects that youths with CD are markedly heterogeneous in their emotion processing (dis)abilities. Specific emotion dysfunction may be clinically relevant for some subgroups of conduct-disordered individuals, but not for the CD population at large[8,9]. Thus, we acknowledge that emotional processes may only partially account for the phenomenon of CD. Other neurocognitive mechanisms, including language processing, social cognition, or hot and cool executive

functions, may play an important contributing role, too[6], and should be examined in future studies.

In conclusion, this large-scale investigation provides compelling evidence for deficient emotion functioning in both conduct-disordered girls and boys across three neurocognitive domains that have previously been linked to CD etiology, including emotion recognition, learning, and regulation. These results were unrelated to potential confounding factors, including common co-occurring psychiatric symptomatologies (e.g., ADHD diagnosis, and number of current ADHD symptoms), IQ differences, CD-onset type, psychotropic medication status, or site. Importantly, we found no clear evidence for a sex-specific neuropsychological profile of emotion dysfunction in females versus males with CD (see[49] for similar observations in ADHD). This finding suggests that neurocognitive models of CD[8] may in fact apply equally to males and females, supporting the assumption that no unique female-tailored account is needed to explain the origin of antisocial behaviors in girls[11]. If emotion dysfunction indeed contributes to the emergence and maintenance of severe antisocial behaviors among both girls and boys, then strategically targeting emotion functioning in clinical and research settings will help in developing more personalized and efficacious treatments. For instance, individual task-based neurocognitive training may help youths develop specific emotion processing skills which, in turn, may improve their responsiveness to behavioral interventions[50]. Whether sex-tailored interventions are warranted to better treat emotion deficits in CD girls versus boys needs to be tested in future studies.

References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*. Washington, DC: American Psychiatric Association; 2013.

2. Foster EM, Jones DE. The High Costs of Aggression: Public Expenditures Resulting From Conduct Disorder. *Am J Public Health*. 2005;95(10):1767-1772.

3. van Goozen SHM, Fairchild G, Snoek H, Harold GT. The evidence for a neurobiological model of childhood antisocial behavior. *Psychol Bull*. 2007;133(1):149-182.

4. Blair RJR, Veroude K, Buitelaar JK. Neuro-cognitive system dysfunction and symptom sets: A review of fMRI studies in youth with conduct problems. *Neurosci Biobehav Rev*. 2018;91:69-90.

5. Frick PJ. Developmental pathways to conduct disorder: Implications for serving youth who show severe aggressive and antisocial behavior. *Psychol Schs*. 2004;41(8):823-834.

6. Rubia K. "Cool" inferior frontostriatal dysfunction in attention-deficit/hyperactivity disorder versus "hot" ventromedial orbitofrontal-limbic dysfunction in conduct disorder: a review. *Biol Psychiatry*. 2011;69(12):e69-87.

7. Frick PJ, Viding E. Antisocial behavior from a developmental psychopathology perspective. *Dev Psychopathol*. 2009;21(4):1111-1131.

8. Blair RJR, Leibenluft E, Pine DS. Conduct Disorder and Callous–Unemotional Traits in Youth. *N Engl J Med*. 2014;371(23):2207-2216.

9. Blair RJR. The neurobiology of psychopathic traits in youths. *Nat Rev Neurosci*. 2013;14(11):786-799.

10. Merikangas KR, He J-P, Burstein M, et al. Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication--Adolescent Supplement (NCS-A). *J Am Acad Child Adolesc Psychiatry*. 2010;49(10):980-989.

11. Moffitt TE, Caspi A. Childhood predictors differentiate life-course persistent and adolescence-limited antisocial pathways among males and females. *Dev Psychopathol*. 2001;13(2):355-375.

12. Silverthorn P, Frick PJ. Developmental pathways to antisocial behavior: the delayed-onset pathway in girls. *Dev Psychopathol*. 1999;11(1):101-126.

13. Bennett S, Farrington DP, Huesmann LR. Explaining gender differences in crime and violence: The importance of social cognitive skills. *Aggression and Violent Behavior*. 2005;10(3):263-288.

14. Gur RC, Richard J, Calkins ME, et al. Age group and sex differences in performance on a computerized neurocognitive battery in children age 8-21. *Neuropsychology*. 2012;26(2):251-265.

15. Zahn-Waxler C, Shirtcliff EA, Marceau K. Disorders of childhood and adolescence: gender and psychopathology. *Annu Rev Clin Psychol*. 2008;4:275-303.

16. Maccoby EE. Gender as a social category. *Developmental Psychology*. 1988;24(6):755-765.

17. Eme RF. Selective Females Affliction in the Developmental Disorders of Childhood: A Literature Review. *Journal of Clinical Child Psychology*. 1992;21(4):354-364.

18. Herpers PCM, Scheepers FE, Bons DMA, Buitelaar JK, Rommelse NNJ. The cognitive and neural correlates of psychopathy and especially callous–unemotional traits in youths:

A systematic review of the evidence. *Development and Psychopathology*. 2014;26(01):245–273.

19. Freitag CM, Konrad K, Stadler C, et al. Conduct disorder in adolescent females: current state of research and study design of the FemNAT-CD consortium. *Eur Child Adolesc Psychiatry*. June 2018:1-17.

20. Dawel A, O'Kearney R, McKone E, Palermo R. Not just fear and sadness: meta-analytic evidence of pervasive emotion recognition deficits for facial and vocal expressions in psychopathy. *Neurosci Biobehav Rev*. 2012;36(10):2288-2304.

21. Calder AJ. Facial Emotion Recognition after Bilateral Amygdala Damage: Differentially Severe Impairment of Fear. *Cognitive Neuropsychology*. 1996;13(5):699-745.

22. Fairchild G, Stobbe Y, van Goozen SHM, Calder AJ, Goodyer IM. Facial expression recognition, fear conditioning, and startle modulation in female subjects with conduct disorder. *Biol Psychiatry*. 2010;68(3):272-279.

23. Fairchild G, Van Goozen SHM, Calder AJ, Stollery SJ, Goodyer IM. Deficits in facial expression recognition in male adolescents with early-onset or adolescence-onset conduct disorder. *J Child Psychol Psychiatry*. 2009;50(5):627-636.

24. Blair RJR, Mitchell DGV, Leonard A, Budhani S, Peschardt KS, Newman C. Passive avoidance learning in individuals with psychopathy: modulation by reward but not by punishment. *Personality and Individual Differences*. 2004;37(6):1179-1192.

25. Byrd AL, Loeber R, Pardini DA. Antisocial behavior, psychopathic features and abnormalities in reward and punishment processing in youth. *Clin Child Fam Psychol Rev*. 2014;17(2):125-156.

26. White SF, Pope K, Sinclair S, et al. Disrupted expected value and prediction error signaling in youths with disruptive behavior disorders during a passive avoidance task. *Am J Psychiatry*. 2013;170(3):315-323.

27. Vitale JE, Newman JP, Bates JE, Goodnight J, Dodge KA, Pettit GS. Deficient behavioral inhibition and anomalous selective attention in a community sample of adolescents with psychopathic traits and low-anxiety traits. *J Abnorm Child Psychol*. 2005;33(4):461-470.

28. Hartung CM, Milich R, Lynam DR, Martin CA. Understanding the relations among gender, disinhibition, and disruptive behavior in adolescents. *J Abnorm Psychol*. 2002;111(4):659-664.

29. Hare TA, Tottenham N, Davidson MC, Glover GH, Casey BJ. Contributions of amygdala and striatal activity in emotion regulation. *Biol Psychiatry*. 2005;57(6):624-632.

30. Leibenluft E. Pediatric Irritability: A Systems Neuroscience Approach. *Trends Cogn Sci*. 2017;21(4):277-289.

31. Hwang S, Nolan ZT, White SF, Williams WC, Sinclair S, Blair RJR. Dual neurocircuitry dysfunctions in disruptive behavior disorders: emotional responding and response inhibition. *Psychol Med*. 2016;46(7):1485-1496.

32. Loney BR, Frick PJ, Clements CB, Ellis ML, Kerlin K. Callous-unemotional traits, impulsivity, and emotional processing in adolescents with antisocial behavior problems. *J Clin Child Adolesc Psychol*. 2003;32(1):66-80.

33. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*. Washington, DC: American Psychiatric Association; 2000.

34. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*. 1997;36(7):980-988.

35. Wechsler D. *Wechsler Intelligence Scale for Children-4th Edition (WISC-IV)*. San Antonio, Texas: Psychological Corporation; 2003.

36. Wechsler D. *Wechsler Adult Intelligence Scale-4th Edition (WAIS-IV)*. San Antonio, Texas: Psychological Corporation; 2008.

37. Wechsler D. *Wechsler Abbreviated Scale of Intelligence (WASI)*. San Antonio, Texas: Psychological Corporation; 1999.

38. Essau CA, Sasagawa S, Frick PJ. Callous-unemotional traits in a community sample of adolescents. *Assessment*. 2006;13(4):454-469.

39. Raine A, Dodge K, Loeber R, et al. The Reactive-Proactive Aggression Questionnaire: Differential Correlates of Reactive and Proactive Aggression in Adolescent Boys. *Aggress Behav*. 2006;32(2):159-171.

40. Rusby J. *Perpetration and Victimization of Relational Aggression Questionnaire, Self-Report*. Eugene, Oregon: Oregon Research Institute; 2009.

41. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Hillsdale, NJ: Erlbaum; 1988.

42. Skovlund E, Fenstad GU. Should we always choose a nonparametric test when comparing two apparently nonnormal distributions? *J Clin Epidemiol*. 2001;54(1):86-92.

43. Moffitt TE, Caspi A, Rutter M, Silva PA. *Sex Differences in Antisocial Behaviour: Conduct Disorder, Delinquency, and Violence in the Dunedin Longitudinal Study*. Cambridge, UK: Cambridge University Press; 2001.

44. Fairchild G, Van Goozen SH, Stollery SJ, Goodyer IM. Fear conditioning and affective modulation of the startle reflex in male adolescents with early-onset or adolescence-onset conduct disorder and healthy control subjects. *Biol Psychiatry*. 2008;63(3):279-285.

45. Euler F, Sterzer P, Stadler C. Cognitive control under distressing emotional stimulation in adolescents with conduct disorder. *Aggress Behav*. 2014;40(2):109-119.

46. Burke JD, Loeber R, Birmaher B. Oppositional defiant disorder and conduct disorder: a review of the past 10 years, part II. *J Am Acad Child Adolesc Psychiatry*. 2002;41(11):1275-1293.

47. Egan GJ, Brown RT, Goonan L, Goonan BT, Celano M. The Development of Decoding of Emotions in Children with Externalizing Behavioral Disturbances and Their Normally Developing Peers. *Archives of Clinical Neuropsychology*. 1998;13(4):383-396.

48. Kendler KS. The super-normal control group in psychiatric genetics: Possible artifactual evidence for coaggregation. *Psychiatric Genetics*. 1990;1:45-53.

49. Gershon J. A meta-analytic review of gender differences in ADHD. *J Atten Disord*. 2002;5(3):143-154.

50. Hubble K, Bowen KL, Moore SC, van Goozen SHM. Improving Negative Emotion Recognition in Young Offenders Reduces Subsequent Crime. *PLoS ONE*. 2015;10(6):e0132035.

Figure titles and legends

Figure 1. Schematic representation of the model-based neuropsychological test battery used to assess: (A) emotion recognition, (B) emotion learning, and (C) emotion regulation, respectively. (A) As an example, the angry-happy facial expression continuum from the *Emotion Hexagon task* is depicted, including the five different morphs from this continuum as well as the six emotion labels used in the task. **(B)** Examples from the *Passive Avoidance Learning task*, depicting one stimulus associated with reward (e.g., gaining 700 points by button press), and one stimulus associated with punishment (e.g., losing 700 points by button press). **(C)** Example layout of the emotion regulation condition from the *Emotion Go/Nogo task*, including neutral expressions as the "go" targets and fearful expressions as the "nogo" non-targets.

Figure 2. Task performance in Conduct Disorder (CD) youths versus typically-developing controls (TDCs) for the three emotion domains tested with the neuropsychological test battery. Relative to TDCs, CD youths demonstrated impairments in: **(A)** emotion recognition across all six basic facial expressions; **(B)** emotional learning, specifically in the learning-from-punishment condition (Note: The total number of errors per condition across all nine blocks is 36); and **(C)** emotion regulation that was accompanied by non-emotional cognitive control deficits. EMM=Estimated Marginal Means; SEM=Standard Error of Mean. ***$p \leq .001$.

Tables

Table 1. Sample characteristics per group and sex.

	CD_f	CD_m	TDC_f	TDC_m	Group-by-Sex	Group (CD/TDC)	Sex (F/M)	Post-hoc comparisons
	n=317	*n*=225	*n*=479	*n*=231	$F^{\#}$	$F^{\#}$	$F/\chi^{2\#}$	*t*-tests[#]
Age (years) *M*(SD)	14.7(2.1)	13.9(2.4)	14.0(2.5)	13.8(2.5)	4.72*	9.10**	12.35***	$CD_f>CD_m=TDC_f=TDC_m$
Estimated IQ *M*(SD)	93.9(12.1)	96.3(12.5)	102.9(12.5)	104.7(11.7)	0.21	146.25***	8.71**	$CD_f=CD_m>TDC_f=TDC_m$
CD total symptoms *M*(SD)	5.4(2.4)	5.5(2.3)	0.03(0.19)	0.07(0.29)	0.08	3462.92***	0.52	$CD_f=CD_m>TDC_f=TDC_m$
Aggression (max. 7)	1.9(1.4)	2.4(1.3)	0(0.1)	0.02(0.1)	23.69***	1791.67***	26.25***	$CD_m>CD_f>TDC_f=TDC_m$
Destruction (max. 2)	0.5(0.6)	0.7(0.6)	0(0)	0.01(0.1)	12.79***	687.48***	15.62***	$CD_m>CD_f>TDC_f=TDC_m$
Deceitfulness/Theft (max. 3)	1.4(0.8)	1.4(0.9)	0.01(0.1)	0.03(0.2)	0.66	1684.21***	0.12	$CD_f=CD_mTDC_f=TDC_m$
Rule violation (max. 3)	1.5(1.1)	1.0(1.0)	0.01(0.1)	0.02(0.1)	45.65***	902.60***	44.77***	$CD_f>CD_m=TDC_f=TDC_m$
CD age-of-onset *n*(%):							40.80***	
Childhood	100(31.5)	133(59.1)						
Adolescence	203(64.0)	86(38.2)						
Unspecified	14(4.4)	6(2.7)						
Current comorbidities *n*(%):								
ODD	243(76.7)	179(79.6)					0.64	
ADHD	95(30.0)	105(46.7)					15.76***	
BPD (DIPD-IV)	63(20.7)	11(5.1)					39.06***	
SUD	61(19.2)	35(15.6)					1.23	
MDD	59(18.8)	24(10.7)					6.91	
PTSD	31(9.8)	8(3.6)					7.63**	
GAD	12(3.8)	5(2.2)					5.67	
Psychotropic meds *n*(%)	81(25.6)	78(34.7)					5.27*	
YPI (CU total score)	31.6(7.5)	34.0(7.8)	25.1(5.5)	29.5(6.3)	1.29	101.12***	19.99***	$CD_f=CD_m>TDC_m>TDC_f$
RPQ (total score)	17.3(8.5)	16.3(8.9)	6.1(4.6)	7.0(4.6)	5.66*	665.04***	0.01	$CD_f=CD_m>TDC_f=TDC_m$
RAQ (total score)	10.2(10.6)	6.7(9.2)	2.9(4.1)	2.4(3.3)	12.13***	181.43***	21.84***	$CD_f>CD_m>TDC_f=TDC_m$

Note: ADHD=attention deficit hyperactivity disorder; BPD=borderline personality disorder; $CD_{f/m}$=female/male conduct disorder; GAD=generalized anxiety disorder; $TDC_{f/m}$=female/male typically developing controls; ICU=inventory of callous-unemotional traits; IQ=estimated intelligence quotient; MDD=major depressive disorder; Meds=on psychotropic medications; ODD=oppositional defiant disorder; PTSD=post-traumatic stress disorder; RAQ= Perpetration and Victimization of Relational Aggression Questionnaire; RPQ= Reactive-Proactive Aggression Questionnaire; SUD=substance use disorder (including substance abuse and dependence); YPI=youth psychopathic traits inventory.
Diagnoses and CD symptoms are based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL). BPD was assessed with the Diagnostic Interview for DSM-IV Personality Disorders (DIPD-IV). For TDC, any current psychiatric diagnosis as well as a history of ADHD, ODD, or CD was exclusionary.
$^{\#}$p-values are based on F-tests (or χ^2-tests,) and follow-up pairwise comparisons with Bonferroni correction.
**p≤.05; **p≤.01; ***p≤.001*