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Baseline autonomic nervous system activity in female children and adolescents with conduct disorder: Psychophysiological findings from the FemNAT-CD study

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ABSTRACT

Purpose: Autonomic nervous system (ANS) functioning has been widely studied in relation to antisocial behavior, such as Conduct Disorder (CD). However, research in females is scarce and findings are inconsistent. This study investigated baseline ANS activity in CD children and adolescents and tested for sex differences. Furthermore, subgroups of CD were investigated: +/- Limited Prosocial Emotions (LPE), +/- comorbid internalizing disorders (INT).

Methods: Baseline ANS activity was measured by Heart Rate (HR), Heart Rate Variability (HRV; parasympathetic activity), Pre-Ejection Period (PEP; sympathetic activity), and Respiration Rate (RR). 659 females (296 CD, 363 controls) and 351 males (187 CD, 164 controls), aged 9–18 years participated.

Results: Baseline HR, HRV and PEP did not differ between CD subjects and controls in both sexes. RR was higher in CD participants than controls amongst females, but not males. LPE was unrelated to ANS activity, whereas females with CD + INT presented lower HRV.

Conclusions: These results suggest that baseline ANS activity is not a robust indicator for CD. However, deviant ANS activity – especially parasympathetic activity - was observed in CD females with internalizing comorbidity.

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The psychophysiological abnormalities observed in this subgroup are indicative of emotion regulation problems. Accordingly, this subgroup may require specific interventions.

1. Introduction

Conduct Disorder (CD) is defined in DSM-5 as a persistent and pervasive pattern of behavior that violates the rights of others or societal norms (American Psychiatric Association, 2013). The diagnostic criteria for CD include aggressive behavior towards other humans and animals, theft, and truancy from school. Gender comparisons clearly indicate that males outnumber females with CD, up to a factor of 10:1 or 15:1 (Kratzer & Hodgins, 1999), although most studies report sex ratios closer to 2:1 or 3:1 (Moffitt & Caspi, 2001). The prevalence of CD amongst females has increased over the past decades (Collishaw, Maughan, Goodman, & Pickles, 2004; Keenan, Loeber, & Green, 1999; Maughan, Rowe, Messer, Goodman, & Meltzer, 2004). As a result, this subgroup has gained the attention of clinicians and researchers. CD females have been found to be at greater risk than their male counterparts for negative outcomes such as school dropout, financial problems, delinquency, substance abuse, mental and physical health problems, teenage prostitution and teenage pregnancies (Schaeffer et al., 2006; Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Moffitt & Caspi, 2001; Tiet, Wasserman, Loeber, McReynolds, & Miller, 2001; Bardone et al., 1998; Loeber & Keenan, 1994). In addition, females appear to differ from males in their clinical presentation of CD and by presenting with higher rates of comorbid internalizing problems (Berkout, Young, & Gross, 2011; Keenan et al., 1999; Keenan & Shaw, 1997; Loeber & Keenan, 1994). Moreover, there is evidence for sex specific correlates of CD – both in terms of environmental (e.g. delinquent peers; Lahey et al., 2006; Gorman-Smith & Loeber, 2005) and neurobiological factors (e.g. genetics; van Hulle, Rodgers, D'onofrio, Waldman, & Lahey, 2007). The neurobiological factor that is considered the most robust correlate of antisocial behavior in children and adolescents is a low resting heart rate (Portnoy & Farrington, 2015; Lorber, 2004; Ortiz & Raine, 2004). However, there are relatively few studies on autonomic correlates (such as heart rate) of antisocial behavior that have included female subjects, and those that did have reported equivocal results (Beauchaine, Hong, & Marsh, 2008; Bubier & Drabick, 2008; Crozier et al., 2008; Kavish et al., 2016). Therefore, this study focused on baseline Autonomic Nervous System activity in females with CD.

The Autonomic Nervous System (ANS) plays a key role in the regulation of physiological responses to environmental challenges, and thus is critically involved in emotional and behavioral regulation (for a review, see Beauchaine & Thayer, 2015). Individual differences in ANS functioning might therefore explain why some children and adolescents are prone to developing psychopathology, whereas others are resilient (McLaughlin, Alves, & Sheridan, 2014). According to the *Low Arousal Theory* children and adolescents that present antisocial behavior, which is the core characteristic of CD, are characterized by lower physiological arousal (e.g. lower heart rate) (Portnoy & Farrington, 2015; Lorber, 2004; Ortiz & Raine, 2004). This association is explained by the *sensation seeking theory* (Raine, 2002; Zuckerman, 1994), which states that individuals with low basal arousal tend to seek out stimulating and risky situations (e.g. criminal activities) in an attempt to increase their arousal levels to an optimal state. In addition, the *fearlessness theory* (Raine, 2002) argues that low arousal is associated with fearlessness, which indicates insensitivity to punishment, and thereby impaired learning from punishment. Results in favour of the *Low Arousal Theory* have been repeatedly replicated (for meta-analyses see Portnoy & Farrington, 2015; Lorber, 2004; Ortiz & Raine, 2004). However, there have also been contradictory results. Several studies did not find deviant arousal levels and others have reported higher arousal levels in children and adolescents presenting antisocial behavior (Schoorl, Van Rijn, De Wied, Van Goozen, & Swaab, 2016; Scott & Weems, 2014; Posthumus, Böcker, Raaijmakers, Van Engeland, & Matthys, 2009; de Wied, Van Boxtel, Posthumus, Goudena, & Matthys, 2009; Calkins, Graziano, & Keane, 2007; Calkins & Dedmon, 2000; Schneider, Nicolotti, & Delamater, 2002; Cole, Zahn-Waxler, Fox, Usher, & Welsh, 1996; Zahn-Waxler, Cole, Welsh, & Fox, 1995; Zahn & Kruesi, 1993). Moreover, most studies on the association between ANS activity and antisocial behavior have been performed in general population samples, displaying various levels of mainly subclinical antisocial and/or conduct problems, which might explain inconsistencies between studies. In addition, sex differences could explain some of these conflicting findings. However, the meta-analyses by Portnoy and Farrington (2015) and Ortiz and Raine (2004) did not identify significant gender differences, although Portnoy and Farrington reported that the association between low arousal and antisocial behavior was weaker amongst females than amongst males. It is important to note that these meta-analyses only included a handful of studies investigating clinically-diagnosed females with CD (Ortiz & Raine: 5 out of 40 studies; Portnoy & Farrtington: 14 out of 115 studies). Other studies that have investigated clinical samples of female adolescents, but were not included in the meta-analyses have shown different results for males and females. For example, Kavish et al. (2016), Beauchaine et al. (2008), and Bubier and Drabick (2008) found significant differences in ANS activity in males, but not in females, and the latter authors even found higher sympathetic nervous system activity in females.

Most studies have focused on heart rate (HR) to measure ANS activity, but HR is a product of the antagonistic effects of its two branches, Sympathetic Nervous System (SNS) activity and Parasympathetic Nervous System (PNS) activity. The SNS and PNS may each have distinct associations with emotional and behavioral regulation, and thus studying SNS and PNS activity separately can better reveal the CD-ANS associations than using a combined measure, such as HR, alone. The SNS is characteristic for high arousal states; it promotes behavioral activation of the individual, such as fight/flight responses, resulting in a higher heart rate. In contrast, the PNS is characteristic for low arousal states; it is activated when the individual is at rest, resulting in a lower heart rate. An adaptive balance between SNS and PNS activity is thought to reflect the ability to effectively respond to both metabolic and behavioral demands (Appelhans & Luecken, 2006; Grossman & Taylor, 2007), whereas deviant SNS and PNS activity is associated with a variety of metabolic, emotional and behavioral regulation problems Grossman & Taylor, 2007; Appelhans & Luecken, 2006). Lower PNS activity is associated with emotional and behavioral problems (Beauchaine & Thayer, 2015; Thayer & Lane, 2009; Thayer & Ruiz-Padial, 2006). This finding also accounts for antisocial behavior in children and adolescents (Beauchaine & Thayer, 2015; El-Sheikh & Erath, 2011). The Polyvagal theory explains this association from an evolutionary perspective, in which the myelinated branch of the vagus nerve (which is one of three main parasympathetic pathways) is assumed to be the newest, and to control the older SNS (Porges, 2007; Porges, 2009). In this light, lower PNS activity indicates less control of the myelinated branch, meaning less inhibition of fight and flight tendencies of the SNS. Since living in contemporary society requires controlled and subtle behavioral responses, and not fight or flight responses, lower PNS activity is believed to lead to emotional and behavioral disruptions. The evolutionary origin of PNS and SNS control over emotions is currently being debated with more and more scientists providing evidence that contradicts the Polyvagal theory (Farmer, Dutschmann, Paton, Pickering, & McAllen, 2016; Gourine, Machhada, Trapp, & Spyer, 2016; Grossman & Taylor, 2007). However, there is a fairly broad consensus that dysregulation of the PNS underlie emotional and behavioral problems. Although less extensively studied, scientific evidence also points to deviant SNS activity in antisocial children and adolescents (; Beauchaine & Gatzke-Kopp, 2012; Crowell et al., 2006), such that both lower PNS and SNS activity are believed to characterize CD.

Various studies have revealed findings in CD subjects that do not support the expected ANS patterns, however. It is suggested that these inconsistencies derive from the high heterogeneity within CD samples (Fanti & Kimonis, 2017). The importance of this heterogeneity has been acknowledged and led to the addition of a specifier for CD in DSM 5. Individuals presenting with at least two out of four callous-unemotional (CU) traits (i.e. limited empathy, lack of guilt, shallow affect, unconcerned about school performance) fulfil the Limited Prosocial Emotions (LPE)-specifier (APA, 2013). Pardini, Stepp, Hipwell, Stouthamer-Loeber, and Loeber (2012) showed that females fulfilling criteria for the LPE specifier present more CD symptoms, more aggression and higher levels of impairment. On the other hand, many psychophysiological studies have not controlled for CU traits or the high level and variety of comorbid problems, or possible gender differences. Fanti and Kimonis (2017) suggests that CU traits and comorbid internalizing disorders can be used to identify subgroups within CD populations that are characterized by distinct arousal profiles: individuals high on CU traits have a lower resting heart rate, whereas those with CD and comorbid internalizing problems have an increased heart rate and sympathetic activity at rest. Both subgroups, however, should show low HRV, indicative of emotion regulation problems. Internalizing comorbidity is high in antisocial females (Keenan et al., 1999), and thus assessing for internalizing disorders and taking this into account during analyses seems important when subtyping a CD female population.

Another general marker for arousal is respiration rate (RR). However, to our knowledge it has rarely been studied in relation to CD. Increased RR is associated with elevated levels of anxiety (Masaoka & Homma, 2004) and with severity of internalizing problems in girls (Henje Blom, Serlachius, Chesney, & Olsson, 2014). Since respiration rate is partially controlled by the limbic system (Masaoka, Izumizaki, & Homma, 2014), which plays an essential role in emotion processing, it is likely to be relevant for CD as well, as there is considerable evidence for emotion processing deficits in CD (Fairchild et al., 2013). Accordingly, RR will be investigated for the first time in CD in this study.

In sum, there is a gap in the literature on ANS functioning in females with CD. Therefore, the aims of this study are to: (1) compare baseline ANS activity in CD females with that of typically-developing females; (2) investigate sex-by-group interactions in baseline ANS activity, and (3) investigate ANS patterns underlying different subgroups of CD females: CD with limited prosocial emotions (LPE+) and CD with comorbid internalizing disorders. This study will thereby contribute to our understanding of the neurobiological mechanisms underlying female CD and might enhance our ability to identify specific subgroups within this heterogeneous group on the basis of psychophysiological activity. Eventually, this might facilitate the identification of different treatment targets in females with CD relative to males. We hypothesized that we would find lower HR, lower PNS activity, and lower SNS activity, but higher respiration rate in females and males with CD as compared to controls. In accordance with the most recent meta-analysis in this field (Portnoy & Farrington, 2015) we expected these effects to be stronger for males than for females. Furthermore, we hypothesized that the subgroup of females with CD and comorbid internalizing disorders would show a differential ANS pattern indicative of increased arousal of ANS dysregulation: higher HR and RR, and lower PNS activity.

2. Method

The current study is part of the ongoing multicenter European FP7 study on the *Neurobiology and Treatment of Adolescent Female Conduct Disorder (FemNAT-CD*; for a description see Freitag, 2014). It was approved by the European Commission and the local ethical committees of all participating sites. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants and their caregivers.

2.1. Recruitment and participants

This study included 1010 children and adolescents (659 females: 296 cases and 363 typically developing controls; 351 males: 187 cases, 164 controls) aged between 9 and 18 years (mean = 14.22, SD = 2.4). The participants were recruited by flyers, advertising in internet forums, through schools, clinics and youth welfare institutions in seven countries (Germany, Greece, Hungary, Netherlands, Spain, Switzerland, United Kingdom). Individuals were classified as cases if they met diagnostic criteria for CD when assessed with the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997). Individuals aged 9–12 years were also classified as cases if they met full diagnostic criteria for Oppositional Defiant Disorder (ODD) and had at least 1 CD symptom, and individuals aged 13+ years when they met criteria for ODD and endorsed at least 2 CD symptoms. Participants were classified as controls if they did not meet criteria for any current psychiatric disorder (besides learning disorders), and were free of CD, ODD, and Attention-Deficit/Hyperactivity Disorder (ADHD) in the past. Exclusion criteria for both controls and cases were: ICD-10, DSM-IV TR or DSM-5 clinical diagnosis of autism spectrum disorder or schizophrenia currently or in the past, current bipolar disorder or mania, known

Table 1
Demographic, cognitive and physical characteristics of the sample.

General characteristics	Female				t	Male				t
	CASE (N = 296)		CONTROL (N = 363)			CASE (N = 187)		CONTROL (N = 164)		
	M	*SD*	*M*	*SD*		*M*	*SD*	*M*	*SD*	
Age	14.8	2.0	13.95	2.5	4.85**	13.95	2.6	14.07	2.6	−0.463
IQ	93.62	11.9	103.58	12.8	−9.94**	96.67	13.8	105.39	11.9	−6.13**
Medication use	33%	0.5	6.6%	0.3	8.64**	33%	0.5	3.6%	0.2	7.75**
BMI	22.7	4.6	20.6	4.1	5.49**	20.7	4.1	20.9	4.3	−0.39
Smoking (cigarettes per day)	6.20	7.1	0.3	2.3	12.52**	5.00	7.7	0.7	2.6	6.02**
Sports (hours per week)	2.9	3.2	4.0	3.9	−3.68**	5.3	5.3	5.6	5.2	−0.44
SES	−0.39	0.9	0.24	1.0	−7.86**	−0.24	0.8	0.42	0.9	−6.61**

Note. SES = Socioeconomic status, BMI = body mass index.
** *t*-test is significant at the < .005 level (two tailed).

monogenetic disorder, genetic syndrome, any chronic or acute neurological disorder, e.g. cerebral palsy, current treatment for epilepsy, history of moderate to severe traumatic brain injury. All participants had to have an IQ of 70 or above. An overview of the general sample characteristics is provided in Table 1.

2.2. Measures

2.2.1. Psychiatric diagnosis

Diagnostic information was obtained using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). The K-SADS-PL is a standardized, semi-structured clinical interview assessing current and past episodes of psychopathology in children and adolescents according to DSM 5 criteria. Interviews were conducted with the participant and a parent or caretaker, in separate rooms to ensure confidentiality. Additionally, where available, information from medical or case files was used. Summary ratings were derived from the clinical judgment using all sources.

Internalizing psychopathology was defined as meeting the DSM-IV criteria for any mood or anxiety disorder: depression, adjustment disorder, disruptive mood dysregulation disorder (DMDD), anxiety disorder, obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD). For analysis on internalizing psychopathology diagnostic information of current episodes was used. Diagnostic information for this sample is provided in Table 2.

2.2.2. IQ

An IQ estimation was done with the WASI (Wechsler, 1999), or in non-English speaking sites by two subtests of the Wechsler Intelligence Scale for Children (WISC; Wechsler, 1991, 2003): vocabulary and block patterns, or, depending on age, the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 2008): vocabulary and matrix reasoning. The raw scores on these subtests were transformed into norm scores, which were summed. Individuals had to achieve a sum score of 7 or higher to be included in the study. In case a participant refused to complete the two subtests, and a valid IQ test had been assessed after the age of 8, the participant could be included when the IQ test revealed a total IQ score > 70.

2.2.3. Limited prosocial emotions (LPE) specifier

We used the Youth Psychopathic traits Inventory (YPI; Andershed, Kerr, Stattin, & Levander, 2002) to assess the LPE specifier, according to the procedure proposed by Colins and Vermeiren (2013). This method appeared effective in identifying CD girls who were more aggressive, and showed higher levels of delinquent and rule breaking behavior (CD + LPE; Colins & Andershed, 2015; Jambroes et al., 2016). The YPI consists of 50 items with a 4-point Likert scale, ranging from “Does not apply at all” (1) to “Applies very well” (4). The YPI is organized into three dimensions of psychopathy: grandiose/manipulative, callous-unemotional (CU) and impulsive/irresponsible. For the purposes of the current study, only the three subscales of the CU dimension were used: unemotionality (e.g., “I usually feel calm when other people are scared”), callousness (e.g., “I think that crying is a sign of weakness, even if no one sees you”) and remorselessness (e.g., “To feel guilt and regret when you have done something wrong is a waste of time”). Each subscale consists of five items. A participant met criteria for one of the CU traits (unemotionality, callousness, remorselessness) when he/she reported that at least one item on the corresponding subscale applied very well to them. Participants were considered to meet criteria for the LPE specifier if two or more CU traits were endorsed to threshold.

2.3. Autonomic nervous system (ANS) assessment

ANS measures were performed using ECG and ICG registration by the VU-AMS device (Vrije Universiteit Ambulatory Monitoring System; de Geus, Van Lien, Neijts, & Willemsen, 2014). H98SG, ECG Micropore electrodes were used, and the skin was cleaned with alcohol before electrode application. The R-peak time series was derived from the ECG data by an automated detection algorithm within the VU-DAMS software package version 3.9 and was checked manually for missed or incorrect R-wave peaks and abnormalities in the registration. Abnormalities were defined as Premature Ventricular Contractions (PVCs) and Premature Atrial Contractions (PACs) or low-quality ECG signal fragments, and were removed from the data. Ensemble averaged ECG and ICG complexes were derived from all valid heartbeats. In the ensemble averaged ECG, the Q-onset was detected and in the ensemble averaged ICG, the B-point, dZ/dt-min peaks and X-points were identified by an algorithm within the VU-AMS software package. All scoring in the ensemble averaged complexes was again checked manually. Data on Respiration Rate was derived from the dZ-signal (thorax impedance). The VU-DAMS software identified ‘irregular respiration’ when deviations in the duration of consecutive breaths reach a threshold. When > 50% of the respiration data was identified as ‘irregular’ Respiration Rate data was set as missing. Data checking and scoring was performed by trained researchers and students, and consensus meetings were organized for complex data.

Heart Rate (HR) in beats per minute (bpm) was derived from the ECG signal derived R-peak time series and Respiration Rate (RR) in breaths per minute (bpm) was derived from the thorax impedance. To obtain measures of Parasympathetic Nervous System (**PNS**) activity, Heart Rate Variability (HRV) was assessed. This was operationalized by Respiratory Sinus Arrhythmia (RSA), i.e. the high-frequency component of HRV. Respiratory Sinus Arrhythmia (RSA) is defined as the longest heart period during expiration minus the shortest heart period during inspiration and is perceived as a reliable indicator for PNS activity (Grossman & Taylor, 2007; Thayer, Åhs, Fredrikson, Sollers, & Wager, 2012). RSA was computed on a breath-to-breath basis. When no difference in shortest and longest beats could be detected, RSA was set to be zero for that particular breath. RSA values were set as missing when > 50% of the breaths could not be detected or were identified as

Table 2
DSM 5 disorders in the sample.

	Female Case (N = 296)	Female Control (N = 363)	Male Case (N = 187)	Male Control (N = 164)
Externalizing disorders				
CD	237 (80.1%)	0	158 (84.5%)	0
ODD	203 (68.6%)	0	139 (74.3%)	0
ADHD	88 (29.7%)	0	88 (47.1%)	0
LPE specifier	102/274 (37.2%)	47/358 (13.1%)	86/173 (49.7%)	33/155 (21.3%)
Alcohol use disorder	18 (6.1%)	0	12 (6.4%)	0
Substance use disorder	46 (15.5%)	0	32 (17.1%)	0
Internalizing disorders				
Any internalizing disorder	96 (32.4%)	0	41 (21.9%)	0
Depression	56 (18.9%)	0	18 (9.6%)	0
Adjustment	7 (2.4%)	0	2 (1.1%)	0
DMDD	6 (2.0%)	0	5 (2.7%)	0
Anxiety	38 (12.8%)	0	18 (9.6%)	0
OCD	5 (1.7%)	0	1 (0.5%)	0
PTSD	27 (9.1%)	0	8 (4.3%)	0
Other				
TIC	1 (0.3%)	0	2 (1.1%)	0
ELIM	8 (2.7%)	0	14 (7.5%)	0
Eating disorder	3 (1.0%)	0	0	0

Note. CD: Conduct Disorder; ODD: Oppositional Defiant Disorder; ADHD: Attention-Deficit/Hyperactivity Disorder; LPE: limited prosocial emotions; DMDD: Disruptive Mood Dysregulation Disorder; OCD: Obsessive Compulsive Disorder; PTSD: Post-traumatic Stress Disorder; TIC: Tic Disorder; ELIM: Elimination disorder (Enuresis/Encopresis).

'irregular' by the VUDAMS software. Respiration rate (RR) can affect RSA independently from PNS activity (Grossman & Taylor, 2007; Ritz & Dahme, 2006; Hirsch & Bishop, 1981) and is therefore included as a covariate when analysing RSA.

Sympathetic Nervous System (**SNS**) activity was measured by the Pre-Ejection Period (PEP; expressed in msec). This is currently the most reliable non-invasive indicator of SNS activity and can be derived from combined ICG and ECG recording (van Lien, Schutte, Meijer, & de Geus, 2013). PEP is defined as the time period between the onset of the left ventricular depolarization and the opening of the aortic valve. These events are marked respectively by the Q-wave onset in the ECG and the B-point in the ICG.

2.3.1. Baseline measurement

After the ECG/ICG electrodes were applied to the participant's body a 10-min habituation period followed. This enabled the participant to become accustomed to the setting in order to minimize the effect of stress induced by the experimental setting. Thereafter a 5-min video was presented to obtain ANS baseline measures. An excerpt from an aquatic video (Coral Sea Dreaming, Small World Music Inc.) was used as the baseline video. This video appeared effective in promoting ANS resting levels in a previous study (Piferi, Kline, Younger, & Lawler, 2000). The video was presented on a DELL Latitude E5550 Laptop and Sennheiser HD 201 earphones were used.

Prior to the physiological assessment, participants were asked whether they had smoked in the past hour, consumed alcohol or used drugs in the past 24 h. If they answered affirmatively to any of these questions, the assessment was postponed.

2.4. Covariates

Covariates of interest in this study were: age, IQ, smoking, sports, medication, BMI, SES (see correlation matrix: Appendix 1). Age, smoking, sports, medication, BMI and SES all have been identified as variables to impact ANS (Hu, Lamers, de Geus, & Penninx, 2017; Piotrowska, Stride, Croft, & Rowe, 2015; Koenig et al., 2014; Licht, Penninx, & de Geus, 2012; Alvarez & Pahissa, 2010; O'Brien & Oyebode, 2003). Furthermore, IQ was added as a covariate since it is generally perceived to correlate with psychopathology. Covariates that showed a significant correlation with the outcome measures were used in the specific analyses. For the analysis on HR, significant covariates were: medication and sports, for the analysis on RR: IQ, medication and smoking, for the analysis on RSA: smoking and respiration rate, for the analysis on PEP: IQ, smoking, sports, BMI. Age was used as a covariate for all outcome measures.

2.4.1. Medication

We assessed current use of psychotropic medication (e.g. Methylphenidate, Fluoxetine) by asking the participant, caretaker, therapist or parent. For the analysis, we treated this as a dichotomous variable (0 = no medication and 1 = medication).

2.4.2. Smoking

We assessed smoking on the day of the physiological assessment by asking the participants "*How many cigarettes do you smoke on an average day?*" (cigarettes/day).

2.4.3. Sports

We asked the participant on the day of the physiological assessment "*How many hours a week do you practice sports?*" (hours/week).

2.4.4. Socioeconomic status

Standardized factor scores for Socioeconomic status (SES) were computed (mean = 0, SD = 1) based on parental income, education and occupation. Assessments were based on the International Standard Classification of Occupations (ISCO-08; International Labour Organisation, 2012) and the International Classification of Education (ISCED; UNESCO, 2015). Due to potential economic variation on the country level, SES was centered and scaled within each country, in order to obtain an indicator of relative socioeconomic position. Reliability (internal consistency) of the composite SES score was acceptable (Cronbach's Alpha = .74).

2.4.5. BMI

BMI was calculated based on height, weight, gender and age.

Participants with missing values on one of these variables were excluded from analyses in which that variable was used as a covariate.

2.5. Statistical analyses

2.5.1. ANS measures

Before analysis, the HR, RR, RSA and PEP data were cleaned and checked for outliers. HR and RR were normally distributed according to Kolmogorov-Smirnov-test. PEP showed a strong deviation from normality. However, after correcting for group, gender, age, sport and smoking the residuals appeared normally distributed. RSA was log-transformed because it showed a right-skewed distribution, and was closer to a normal distribution after transformation. Values deviating from the group mean by ± 3 SD were classified as outliers and excluded. For HR 7 outliers were identified and one value was missing due to technical problems. For RR there were 5 outliers and 6 missing values because they reached the threshold of 50% of irregular respiration. Accordingly, this resulted in 6 missing values for RSA. There were 8 outliers detected for RSA, 1 outlier for PEP and 50 PEP values were set as missing based on manual inspection of the ECG/ICG complexes. Subsequently, we checked if these excluded values differed in a

Table 3

Means and standard deviations for the four psychophysiological parameters and statistical outcomes of group comparisons and interaction effects using analysis of covariance.

	Female				Male				Statistical comparisons		
	Case		Control		Case		Control				
	(N = 296)		(N = 363)		(N = 187)		(N = 164)		Sex	Group	Sex × Group
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	F	F	F
HR (bpm)	78.52	10.96	78.14	10.79	77.08	12.01	74.64	11.99	12.05**	1.889	.35
RR (bpm)	18.23	2.40	17.41	2.47	18.11	2.44	17.74	2.46	.066	1.443	4.054*
RSA[1] (msec)	1.85	0.23	1.88	0.22	1.87	0.24	1.88	0.24	.179	.507	.575
PEP (msec)	103.95	17.68	100.62	17.09	96.36	21.27	94.93	20.83	19.43**	.383	.63

Note. HR = heart rate, RR = respiration rate, RSA = respiratory sinus arrhythmia, PEP = pre-ejection period; 1 RSA values are log transformed.

* Significant at the .05 level.

** Significant at the .01 level (two tailed).

systematic way between groups (gender and case/control status). Summing up the number of missing values and outliers for all four ANS measures per individual, an ANOVA was performed and showed no difference between the groups.

This was a multicenter study and thus we conducted several analyses in order to test for potential site effects on ANS measures. However, when controlling for sample composition, no significant site effects were detected using ANOVA and regression analysis.

2.6. Statistical analyses

Two by two between-groups analysis of covariance were conducted to assess the effect of CD and gender on of each of the psychophysiological parameters (HR, RR, RSA, PEP). Group (case/control) and gender were used as independent variables and the psychophysiological parameter was set as dependent variable. To investigate sex differences, the interaction term sex * group was added to each model. Only those covariates that were significantly associated with the specific dependent variable were entered.

For the subgroup analyses, the effect of the LPE specifier was investigated by a 2 × 2 between-groups (case/control-status and LPE-specifier) analysis of covariance for the sexes separately. The second subgroup analysis concerned comorbid internalizing psychopathology (INT). Since internalizing psychopathology was an exclusion criterion for control participant, analysis of covariance was performed comparing 3 groups: controls, cases with a current internalizing disorder (CD + INT), and cases without a current internalizing disorder (CD-INT), for females and males separately.

Probabilities of all tests were two-tailed and a significance level of 0.05 was used. The Bonferroni correction was applied when post-hoc analyses were run with the ANOVA.

3. Results

Table 3 presents the mean values and standard deviations for the four psychophysiological parameters that were assessed during the baseline assessment, split by group and gender, together with the results of statistical comparisons.

To compare the four psychophysiological measures between cases and controls, 2 × 2 between-groups (case/control-status and sex) analyses of covariance were performed for resting heart rate (HR), Respiration Rate (RR), Respiratory Sinus Arrhythmia (RSA) and Pre-Ejection Period (PEP). There were significant main effects of sex on HR (F(1,782) = 12.051, $p < 0.01$, ηp2 = 0.015)) and PEP (F (1,600) = 19.429, p < 0.01 (ηp2 = 0.031)), indicating that females had higher HR and longer PEP values than males. The analyses of covariance did not show a significant main effect of group on heart rate (HR), Respiration Rate (RR), Respiratory Sinus Arrhythmia (RSA) or Pre-Ejection Period (PEP). The interaction term sex*group was significant only for RR (F(1,782) = 4.054, $p < 0.05$, ηp2 = 0.005). Post hoc tests revealed that female cases had a significantly higher RR than female controls (F(1,539) = 5.256, p < 0.05, ηp2 = 0.010), whereas male cases and controls did not differ from each other (F (1,239) = 0.876, $p = .35$, ηp2 = 0.004); see Fig. 1.

3.1. Differences between CD subtypes

3.1.1. Limited prosocial emotions specifier

The Limited Prosocial Emotions (LPE) specifier could not be assessed in 27 females (4.1%) and 23 males (6.6%) due to missing data. The overall prevalence of the LPE specifier was lower in controls than in cases (X^2 (1, $N = 960$) = 81.82, $p < .05$). And as expected the prevalence was higher in males than in females (X^2 (1, N = 960) = 16.69, p < .05), which accounted for both the case (X^2 (1, $N = 447$) = 6.28, p < .05) and control group (X^2 (1, $N = 513$) = 4.87, p < .05). The LPE specifier was met by 102 female cases (37.2%) to 86 male cases (49.7%), and by 47 female controls (12.9%) to 33 male controls (20.1%). A 2 × 2 (case/control status, ± LPE specifier) between-groups analyses of covariance was performed for both sexes separately, controlling for covariates. No significant main effects or interaction effects were detected for HR, RR, RSA, and PEP for both females and males. We also conducted a three-group analysis of covariance in which we applied the LPE specifier only to cases and not to controls, since its purpose is to distinguish within CD individuals (APA, 2013). This revealed a significant effect for RR in females (F(2,524) = 2.988, $p = 0.05$, ηp2 = 0.011) which was not found in males. Post-hoc tests revealed that CD females who did not meet the LPE specifier (CD-LPE) had a significantly higher RR than female controls. The LPE-specifier did not differentiate within the CD group (see Fig. 2). Given the sample sizes and the closeness of the mean values (CD-LPE: $N = 140$, RR = 18.29; CD + LPE: $N = 84$, RR = 18.37), we assume that the significant difference in RR between CD-LPE and control females is similar to the main effect of case/control status on RR that was found in females.

3.1.2. Comorbid internalizing disorders

For the purposes of this study, we considered depression, adjustment disorder, disruptive mood dysregulation disorder, anxiety disorder, obsessive compulsive disorder, and post-traumatic stress disorder as internalizing disorders. Data on internalizing disorders were missing for 22 female cases and 9 male cases, thus these individuals were excluded from the analyses. Ninety-six (32.4%) female cases and 41 (21.9%) male cases fulfilled the diagnostic criteria for at least one current internalizing disorder. As controls by definition did not meet diagnostic criteria for any internalizing disorder, we ran a three-group analysis of covariance to explore the impact of comorbid internalizing disorders on the different psychophysiological parameters for males and females separately. Heart Rate (HR), Respiration Rate (RR), and Pre-Ejection Period (PEP) were not affected by internalizing psychopathology in either females or males. However, the analysis revealed a significant group effect on RSA in females (F(2,536) = 3.847, $p < 0.05$, ηp2 = 0.014). Post-hoc tests revealed that female cases with a comorbid internalizing disorder (CD + INT) had significantly lower RSA values than female cases without a comorbid internalizing disorder (CD-INT; F(1,221) = 5.211, p < 0.05), respectively 1.76 (SD: 0.25), and 1.86 (SD:0.26; see Fig. 3). The partial eta squared was 0.023 indicating a small effect. This effect remained statistically significant after controlling for respiration rate.

We repeated the above analyses using *lifetime* diagnoses of comorbid internalizing disorders instead of *current* diagnoses. Statistical comparisons revealed the same results.

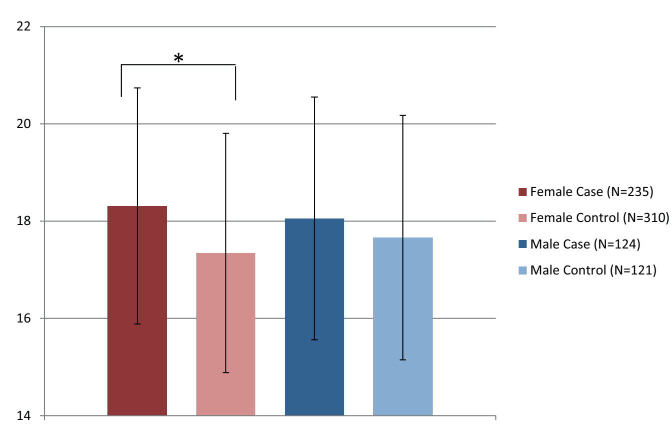

Fig. 1. Respiration Rate (RR) in beats per minute (bpm) in CD Females and Female Controls, CD Males and Male Controls.
Note. Error bars show standard deviations, and * indicates significance at the .05 level.

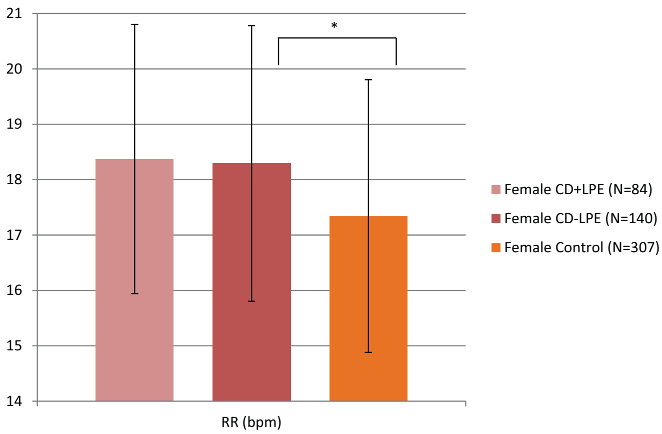

Fig. 2. Respiration Rate (RR) in CD Females fulfilling the LPE Specifier (CD + LPE), CD Females not fulfilling the LPE Specifier (CD-LPE), and Female Controls.
Note. Error Bars show Standard Deviations, and * indicates significance at the .05 level.

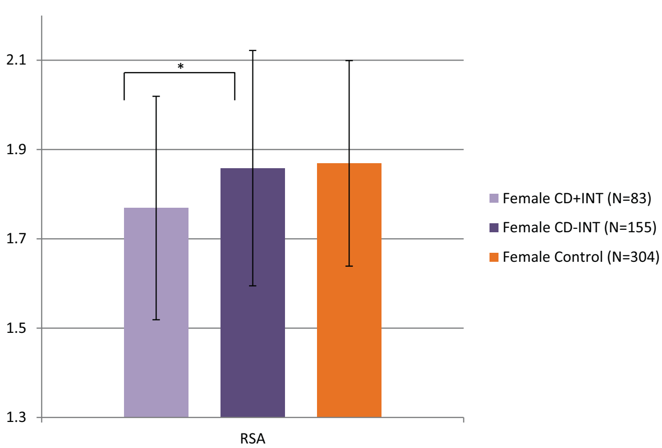

Fig. 3. Respirator Sinus Arrhythmia (RSA) in CD Females with a Comorbid Internalizing Disorder (CD + INT), CD Females without a Comorbid Internalizing Disorder (CD-INT), and Female Controls.
Note. Error bars show standard deviations, and * indicates significance at the .05 level.

Since IQ is theoretically unrelated to ANS measures we have run all analysis that included IQ as covariate again leaving out this covariate. All results remained unchanged.

4. Discussion

This study aimed to compare CD females and males with their typically-developing peers in terms of basal autonomic nervous system (ANS) activity, and to investigate sex differences and similarities in the relationships between CD and ANS activity, as well as potential (sex-specific) differences between subtypes of CD. Group-wise comparisons revealed that females with CD did not differ from typically developing females in baseline heart rate (HR), Respiratory Sinus Arrhythmia (RSA) and Pre-Ejection Period (PEP), although they did show a higher respiration rate (RR). Males with CD did not differ from typically developing males on any of the psychophysiological measures. Except for the effect on RR in females, the current results are in contrast with our hypotheses that CD would be associated with low arousal. Similarly, we did not find any support for our hypotheses regarding the Limited Prosocial Emotions (LPE) subtype of CD. Subgroup analysis revealed that the LPE specifier did not differentiate subtypes within CD females and CD males based on psychophysiological measures. However, as expected, deviant ANS activity was detected in a subgroup of CD females who presented with comorbid internalizing disorders. This subgroup showed lower RSA values (i.e. lower parasympathetic activity) than CD females without such comorbidity. This effect was not observed in males.

Our findings do not support the *Low Arousal Theory*, which proposes that antisocial individuals show lower arousal than controls, but we did not find a lower heart rate in either CD females or CD males. We had expected to find lower levels of parasympathetic activity (i.e. lower RSA), indicating difficulties in regulating emotions and behaviour, and lower sympathetic activity (i.e. lengthened PEP) in CD children and adolescents. These hypotheses were not supported either. To understand the current findings, which contrast with previous literature, several aspects have to be acknowledged. First of all, most studies investigating the L*ow Arousal Theory* have included community samples. These findings may not be representative for clinical samples that show high levels of impairment in multiple aspects of functioning. Second, Portnoy and Farrington (2015) noted that the association between heart rate and antisocial behavior was stronger in earlier publications, and has become weaker in more recent publications. The findings from the current study, in a large sample of CD girls and boys, fit with this trend. Furthermore, this study showed that controlling for several covariates is highly important when investigating psychophysiological functioning. Prätzlich et al. (2018; (in this volume)) highlight the importance of controlling for smoking when relating ANS functioning to antisocial behavior. Previous studies have not included covariates in a consistent manner: Portnoy and Farrington describe that only 26 of the 115 studies in their meta-analysis included covariates, and only a few accounted for smoking status. This might have affected previous findings considerably. In this light, we want to mention that one of our covariates, medication use, was a dichotomous covariate and therefore the effect of type and dose of medication could not be assessed.

Notably, respiration rate (RR) was higher in females with CD than in typically developing females. Higher RR was previously reported to be associated with internalizing problems before (Henje Blom et al., 2014; Masaoka & Homma, 2004), but its association with externalizing problems was unknown. Our results suggest that RR could be an indicator for general emotion regulation problems, and not solely for internalizing problems, but further research is necessary to test this hypothesis. We recommend that future studies focus on this measure since it is easily recorded, and could be used as both an indicator for those at risk for emotion regulation problems and as a target for interventions. Several studies have shown that breathing exercises decreased self-reported feelings of tension and anxiety in both a community sample (Masaoka & Homma, 2004) and a clinical sample (subjects with alcohol dependency; Clark & Hirschman, 1990). RR might therefore be a promising target.

As for subgroups of CD, the LPE specifier did not distinguish CD subgroups with differing ANS profiles, and this was true in both females and males. The LPE specifier is believed to indicate a more homogeneous subgroup of children and adolescents that present severe and persistent antisocial behavior, which stems from neurobiological deficits, such as arousal deficiencies (Frick, Ray, Thornton, & Kahn, 2014). However, this study did not find differences between LPE+ and LPE- individuals with CD in any measure of ANS activity. Several remarks should be made before conclusions can be drawn. First of all, the LPE specifier was generated based on self-report. In general, this is associated with reporting bias, which might have affected our results. However, van Damme, Colins, and Vanderplasschen (2015) showed that the LPE specifier identified a group of seriously antisocial girls, but only when using self-report and not when using parent-report. This suggests validity of the self-report measure that we used to assess the LPE-specifier. In addition, we used the LPE specifier as a categorical variable, in line with the DSM-5. Colins and Andershed (2015) presented evidence that this approach identifies a more severe subgroup of female children and adolescents. Still, using a dimensional approach may provide more information on its relation with ANS functioning and this should be examined in future studies. See Prätzlich et al., 2018 (in this volume) for results of a dimensional approach in this sample.

The second clinical subgroup describes CD children and adolescents with a comorbid internalizing disorder. This comorbidity was highly prevalent amongst females and this study revealed its effect on psychophysiological functioning over and above externalizing psychopathology. Internalizing disorders appeared to be associated with lower heart rate variability (HRV) in CD females, indicating decreased parasympathetic activity. From the literature, it seems that decreased HRV can be perceived as a robust indicator for both internalizing and externalizing emotion regulation problems (Beauchaine & Thayer, 2015; Graziano & Derefinko, 2013; Beauchaine, Gatzke-Kopp, & Mead, 2007). Support for this association comes from studies showing that PNS activity is regulated by the prefrontal cortex (PFC) (Beauchaine & Thayer, 2015; Thayer, Hansen, Saus-Rose, & Johnsen, 2009). The PFC is associated with executive functions, such as planning, attention, and inhibition, which play a major role in the regulation of emotions and behavior. Therefore, low PNS activity, indicative of PFC dysfunction, would characterize individuals prone to emotion and behavior regulation problems. Considering the results of the current study, either low HRV should be perceived as an indicator of internalizing problems specifically, or CD is not characterized by emotion regulation problems per se, whereas internalizing disorders are. Since the prevalence of internalizing disorders in antisocial populations is high Polier, Vloet, Herpertz-Dahlmann, Laurens, & Hodgins, 2012; Keenan et al., 1999), previous findings showing deviant HRV in externalizing individuals, could have been driven by comorbid internalizing conditions. The effect of internalizing comorbidity emerged only in females, suggesting a sex specific mechanism. Internalizing disorders have an overall higher prevalence in females than in males, and previous studies on HRV and internalizing psychopathology have provided findings that are consistent with as ours (Koenig, Kemp, Beauchaine, Thayer, & Kaess, 2016). Thus, it seems that HRV patterns associated with internalizing psychopathology can be generalized to female CD populations. The accumulating evidence for HRV as a neurobiological marker for emotion regulation problems indicates that HRV potentially can be used as a target for both diagnostics and treatment evaluation. Kemp and Quintana (2013) already described that several non-pharmacological interventions were able to increase HRV significantly, and thus confirms its potential for use in diagnostics and evaluation. This should be investigated more thoroughly in future studies.

To our knowledge, this is the largest study on psychophysiological functioning in a clinical sample of females displaying severe antisocial behavior, in which baseline ANS activity was assessed in a standardized and validated manner. However, several limitations should be noted. We only included a baseline measurement to assess psychophysiological functioning. This could have limited our results since several studies have described that deviant ANS functioning is more pronounced when assessing ANS reactivity (Schoorl et al., 2016; Fairchild et al., 2008). Therefore, we strongly recommend that future studies include a reactivity assessment to investigate ANS functioning more thoroughly and gain a better understanding of the neurobiological mechanisms underlying CD in children and adolescents. Second, only two approaches were used for subtyping. In accordance with DSM-5 and previous literature (Fanti & Kimonis, 2017), we included the LPE specifier and internalizing disorders to differentiate clinically relevant subgroups. There is evidence suggesting that CU traits and internalizing psychopathology should be considered jointly. Euler et al. (2015) identified three groups of CD subjects: CD without CU traits, CD with moderate CU traits combined with anxiety, and CD without anxiety but severe CU traits. Similar results were presented by Fanti and Kimonis (2017). Using these variables dichotomously and independently, as we did, might obscure interactions between these factors. Moreover, Wilson and Scarpa (2012) argue that it is essential to include interactions between biological and social influences to explain externalizing behavior. Therefore, we propose that future studies include biology * psycho/social interaction terms. Furthermore, it is important that future studies focus on other relevant variables that could identify subgroups, such as a forms of aggression, traumatic experiences and different facets of psychopathic tendencies (Schoorl et al., 2016; Zhang & Gao, 2015; Raine, Fung, Portnoy, Choy, & Spring, 2014; Scarpa, Tanaka, & Chiara Haden, 2008; Stadler, Poustka, & Sterzer, 2010; Polman, de Castro, Koops, van Boxtel, & Merk, 2007), and we would recommend including respiration rate in future studies in CD populations.

In conclusion, the current study suggests that ANS functioning, especially heart rate, may not be such a robust correlate of antisocial behavior as has been proposed. However, it did provide evidence for an association between CD and respiration rate, although this was only present in females. To our knowledge, RR has not been studied before in relation to antisocial behavior, but could be a promising psychophysiological marker. Furthermore, we found evidence for an association between ANS activity and internalizing psychopathology in females with CD. Our results suggest that it is important to assess for comorbid internalizing disorders in children and adolescents with CD because it identifies a subgroup that shows distinct autonomic impairments. This may be related to emotion regulation difficulties and therefore may identify a group that is in need of specific interventions. It is increasingly recognized that studying psychophysiological functioning can shed light on the development and persistence of severe antisocial behavior in children and adolescents. Furthermore, psychophysiological measures may be helpful tools in psychoeducation, diagnostics and treatment evaluation. Since these measures can be perceived as fairly objective we think that they are of additional value to the arsenal of tools that professionals currently use in their daily practice. Especially in populations with antisocial behavior, using more objective measures might enhance insight in their behavioral responses and increase patients' receptiveness towards treatment. More research is needed to increase our knowledge on this and to obtain measures that can be directly and practically implemented in clinical practice.

Competing interest

Prof. Dr. Freitag has served as consultant for Desitin and Roche on Autism Spectrum Disorder. She receives royalties for books on ASD, ADHD, and depressive disorder. Dr. de Brito has received speaker fees from the Child Mental Health Centre and the Centre for Integrated Molecular Brain Imaging. All other authors declare that there is no potential conflict of interests.

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