Psychophysiological activity and reactivity in children and adolescents with conduct problems: A systematic review and meta-analysis

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ABSTRACT

The aim of this study was to conduct a systematic review of the literature and meta-analysis to estimate the association between psychophysiological activity and reactivity at baseline or after a psychological task with conduct problems (CP) among children and adolescents. We systematically reviewed published studies reporting autonomic nervous system activity in youth with CP and meta-analyzed the relationship between CP and autonomic baseline as well as task-related reactivity in 66 studies (N = 10,227). Across 34 included case-control studies that were based on CP cut-off scores, we found a significant pooled effect for task related Skin-Conductance, Respiratory Sinus Arrhythmia, and cardiac Pre-Ejection Period, but no significant group differences for Heart Rate nor for any baseline measures. Findings suggested reduced parasympathetic and sympathetic reactivity to emotional tasks, pointing to co-inhibition of the two systems. However, across 32 studies with correlational design we only found a significant negative correlation of baseline and task-related heart rate with CP. The present meta-analysis derived several conclusions that have the potential to inform biological vulnerability models and biologically driven interventions.

1. Introduction

Youth with conduct problems (CP; i.e., symptoms of conduct disorder and oppositional defiant disorder) engage in multiple antisocial behaviors such as bullying others, vandalism, lying, stealing, and excessive arguing with adults (American Psychiatric Association, 2013; Frick and Morris, 2004; Moffitt et al., 2008). CP behaviors place youth on a developmental pathway of low academic achievement, poor peer and parent relations, and delinquent and criminal behavior (Coie and Dodge, 1998; Keiley et al., 2003), resulting in high personal and societal costs. Thus, from a public health standpoint, it is imperative to understand the etiology of CP, in order to inform evidence-based interventions. In the last three decades, several studies investigated the link between abnormal autonomic activity and CP in children and

adolescents. This evidence has the potential to shed light on the developmental mechanisms leading to antisocial behavior as well as the identification of individuals at risk for CP (e.g., Beauchaine, 2012; Blair, 2001; Fanti, 2018; Raine, 1993). Findings from physiological studies might also inform current efforts toward research domain criteria based on biomarkers of psychological disorders (Insel et al., 2010). However, existing findings and theories regarding the physiological activity of children and adolescents with CP are contradictory, pointing to either lower or higher autonomic activity among children and adolescents with CP compared to controls (Fanti, 2018). Therefore, there is a need of a quantitative evidence synthesis via a systematic review and meta-analysis that compares distinct measures of autonomic activity as well as baseline and task-related activity. This is of great importance since the last related meta-analysis was published more than a decade ago

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(Lorber, 2004). Additionally, due to pathophysiological heterogeneity in CP (Fanti, 2018), it is important to establish to which extent differences in personality traits and comorbid psychopathology modify the association between CP and abnormal autonomic responses.

1.1. Physiological measures associated with CP

Youth with CP show deficits in physiological activity in response to emotional stimuli, known to be associated with the Autonomic Nervous System (ANS) (Fanti, 2018; Matthys et al., 2013). Measures of heart rate (HR) and electrodermal activity or skin conductance (SC) have been used in both correlational and case-control studies of CP to explain these deficits. HR and SC activity are important for understanding antisocial behavior because they are both associated with motivational systems involved in the control of behavioral responses to external stimuli (Lorber, 2004). Further, HR and SC are stress regulating mechanisms that prepare the body for fight or flight responses, and as such are important for understanding CP and aggressive behaviors (Fanti, 2018; Raine and Jones, 1987). Although both measures are associated with general emotional arousal, SC is primarily controlled by the Sympathetic Nervous System (SNS), while HR is influenced by both the SNS and the Parasympathetic Nervous System (PNS) (Janig and McLachlan, 1992; Norman et al., 2014). Heart Rate Variability (HRV; i.e., the variation of the period between consecutive heartbeats) is an additional index of ANS activity and relates to emotion regulation (Fanti, 2018). Increased SNS or decreased PNS activity result in heartbeat acceleration and reduced HRV, while a low SNS activity or a high PNS activity can lead to heart beat deceleration (Acharya et al., 2006; Hansen et al., 2007; Thayer and Lane, 2000).

Low baseline HR and SC as well as low HR and SC reactivity in response to negative emotional cues, which are indicators of hypo-arousal, have been identified among youth with CP as well as in adolescents later convicted for crimes (Raine et al., 1997, 1990; van Bokhoven et al., 2005, van Goozen, 2000). However, according to a recent review of the literature (Fanti, 2018) some studies did not reveal any significant associations between HR and SC measures with CP, while additional work indicated that youth with CP show physiological hyper-reactivity and high levels of HR and SC both at rest and in response to negative and fearful emotional stimuli. These contradicting findings point to two distinct possibilities, suggesting that youth at risk for CP might either score on the low (i.e., hypo-arousal) or high (e.g., hyper-arousal) extremes in terms of their HR and SC responses to emotional stimuli. Such mixed findings are problematic and can be clarified in the context of a meta-analysis. Indeed, a meta-analysis conducted more than a decade ago (Lorber, 2004) suggested that greater HR activity is associated with CP, although there was considerable heterogeneity in effect sizes ranging from –1.24 to 0.49 across studies. On the other hand, the narrative review by Fanti (2018) suggested that the majority of studies point to low SC activity during emotional tasks among youth with CP; however, associations with HR were not as consistent. Additionally, although reduced HRV is associated with emotional dysregulation, which place youth at higher risk for CP, prior work resulted in inconsistent findings when comparing antisocial and non-antisocial youth, identifying either no differences, lower or higher HRV when comparing these groups (see Fanti, 2018 for a review). Taken together, these findings suggest differential associations of CP with HR and SC measures, and the need for additional work to clarify the direction of these differences in order to better understand the mechanisms that contribute not only to ANS related measures but also to their developmental pathways.

Because HR is influenced by both autonomic branches, it is important to investigate both sympathetic and parasympathetic systems associated with cardiac activity. Respiratory sinus arrhythmia (RSA; i.e., the variation of HR occurring during the respiratory cycle) is an index of parasympathetic cardiac control, and reflects a vagally mediated modulation of HR such that it increases during inspiration and decreases during expiration. Further, RSA responds to two different regulatory systems. During normal conditions, a coordinated respiratory rhythm in heart rate activity facilitates oxygen diffusion,

whereas during threatening or stressful conditions respiratory rhythm and RSA are suppressed (Porges, 2001). Moreover, RSA relates to the ability to regulate emotions (Beauchaine et al., 2001; Grossman & Wientjes, 1986; Porges and Byrne, 1992). Low resting RSA (i.e., low vagal tone) and greater RSA withdrawal, reflected in reduced RSA reactivity to a stressor, is associated with maladaptive parasympathetic activity, poor emotion regulation, and increased risk of fight or flight responding (Beauchaine et al., 2001; Beauchaine, 2015). Indeed, children and adolescents high on CP exhibit low baseline RSA and reduced RSA reactivity (i.e., greater RSA withdrawal and parasympathetic inhibition) in response to emotional stimuli, associated with emotion dysregulation, loss of regulatory control and increased risk of fight or flight responses (Beauchaine et al., 2008, 2001; de Wied et al., 2006; El-Sheikh and Hinnant, 2011; Gatzke-Kopp et al., 2015; Mezzacappa et al., 1997; Pang and Beauchaine, 2013).

In contrast, the cardiac pre-ejection period (PEP; the systolic time interval) is an index of sympathetic cardiac activity and reflects the time between depolarization of the left ventricle and opening of the aortic valve (Brenner and Beauchaine, 2011). A shorter PEP suggests higher contractility and greater sympathetic tone and has been associated with the start of a stress reaction (Berntson et al., 1994a,b) as well as with reward sensitivity (Tenenbaum et al., 2018). Beauchaine et al. (2001) provided evidence that adolescents with comorbid CD and ADHD symptoms exhibited longer PEP at baseline and less or decreased PEP reactivity to reward than those in ADHD-only or control groups. Both longer PEP at baseline and low PEP reactivity point to less sympathetic cardiac activity among those at risk for CD. This finding has been replicated among preschool children with Oppositional Defiant Disorder (Crowell et al., 2006) and children high on aggression and CP (Beauchaine et al., 2008).

Thus, differential effects of SC, RSA and PEP reactivity denote both sympathetic and parasympathetic functional deficits, and indicate that it is important to investigate the co-activation of both nervous systems to understand CP. For example, even though parasympathetic and sympathetic systems serve opposing physiological functions, it was suggested that co-inhibition, which refers to decreased sympathetic and parasympathetic activity, or co-activation, which refers to increased activity of both branches, characterize child externalizing problems (El-Sheikh et al., 2009). We expect findings from the meta-analysis to inform this line of work and point to multisystemic physiological vulnerability factors.

1.2. Accounting for CP heterogeneity and individual differences

Studies assessing HR and SC at rest or in response to emotional stimuli among children with CP point to contradicting evidence supporting either physiological hypo-arousal or hyper-arousal. Based on these findings we can argue for the existence of heterogeneous CP groups, scoring on opposite extremes on physiological measures of arousal. Indeed, according to Fanti (2018), heterogeneity in CP can explain inconsistencies in physiological reactivity. Prior theoretical and empirical work suggests that the combination of conduct problems with either callous-unemotional (CU; i.e., lack of empathy, absence of guilt, shallow or deficient emotions) traits, internalizing symptoms such as anxiety, or symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD) can result in more severe behavioral profiles (Fanti & Henrich, 2010; Frick et al., 2014a; Lynam, 1996). As a result, examining co-occurrence between CP with CU traits, internalizing problems, and ADHD symptoms in relation to physiological measures can enhance our understanding of these higher risk subgroups of youth and inform CP heterogeneity.

Studies taking co-occurring ADHD symptoms into account suggested that boys with CP irrespective of comorbid ADHD symptoms exhibit lower SC and HR responses to negative emotional stimuli compared to healthy controls (Herpertz et al., 2005, 2003; Herpertz et al., 2001; Northover et al., 2016; Zahn and Kruesi, 1993). Furthermore, Beauchaine et al. (2001) found that children with a combination of CP and ADHD symptoms show lower baseline SC compared with controls, although the association between low

baseline HR with CP was independent of the effects of ADHD symptoms (Scarpa and Raine, 1997). Additional work suggested that low HR and SC activity during emotional stimuli is associated with CP but not ADHD symptoms (McBurnett et al., 1993; Posthumus et al., 2009; Raine and Jones, 1987). In contrast, Waschbusch et al. (2002) found that children high on both CP and ADHD showed greater HR reactivity to emotional provocation compared to antisocial children with no ADHD symptoms. Thus, the majority of prior research suggests that children with comorbid CP and ADHD symptoms show similar physiological dysfunctions as CP youth without ADHD symptoms or that ADHD symptoms do not account for the association between CP and physiological measures. A sub-group meta-analytical approach to investigate the influence of this potential moderator seems an obvious way to validate these findings.

Regarding internalizing problems, findings suggest that youth scoring high only on CP differ from those with comorbid CP and internalizing symptoms by being less reactive to negative situations with lower emotional arousal (Garralda et al., 1991; McBurnett et al., 1993). Indeed, non-anxious antisocial youth exhibit lower SC and HR at rest and reactivity when compared to children and adolescents with either internalizing problems alone or with comorbid externalizing and internalizing problems (Beauchaine et al., 2000; Garralda et al., 1991; Rogeness et al., 1990; Schoorl et al., 2015). It was suggested that levels of anxiety and stress reactivity might explain the distinct physiological reactions to emotional stimuli (i.e., hypo- versus hyper-reactivity) identified in prior work (Fanti, 2018).

Findings from studies taking CU heterogeneity into account suggest that children scoring high on CP and low on CU traits exhibit higher baseline HR and low HR and SC activity in response to negative emotional stimuli compared to those high on both CP and CU traits (Anastassiou-Hadjicharalambous and Warden, 2008; de Wied et al., 2012; Kimonis et al., 2008; Muñoz et al., 2008a,b; Northover et al., 2016). In addition, children and adolescents scoring high on CP and CU score lower on baseline RSA compared to youth high only on CP (de Wied et al., 2012; Mills-Koonce et al., 2015; Wagner et al., 2017). As a result, the co-occurrence between CP and CU traits may explain prior inconsistencies pointing to distinct CP groups differentiated on emotion regulation or showing either hypo- or hyper-arousal. The importance of CU traits in identifying a unique subgroup of children at risk for severe CP has led to their inclusion as a Limited Prosocial Emotions (LPE) specifier for the diagnosis of Conduct Disorder (CD) in the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5; American Psychiatric Association, 2013). In general, evidence for the co-occurrence between CP with ADHD, CU traits, and internalizing psychopathologies suggest that by taking into account these individual differences, especially in the context of a meta-analysis, we might be able to explain prior contradicting findings.

1.3. Current study

The overarching aim of this study is to conduct a systematic review of the literature and meta-analysis to estimate the association between different measures of psycho-physiological activity and reactivity, on the one hand, and CP, on the other hand, among children and adolescents. Building on and extending a previous meta-analysis (Lorber, 2004) as well as a systematic review (Fanti, 2018), we further aimed to explore possible moderators of the association between CP and physiological measures by means of subgroup meta-analyses. Specifically, co-occurring psychopathology (i.e., ADHD and internalizing symptoms) and CU traits were considered. This might uncover differential relations between physiological measures based on different subtypes of CP. Finally, as studies investigating sex differences found that girls exhibit greater autonomic activity than boys (Beauchaine et al., 2008), which might be another factor influencing the findings of studies using samples of boys and girls, we also tested for sex differences in the subgroup meta-analyses.

The present meta-analysis is concerned specifically with the association between physiological cardiac systems of arousal and

regulation, including HR, HRV, PEP and RSA, with CP among youth. We also included studies that assess tonic (skin conductance level: SCL) or phasic components (Skin Conductance Responses: SCRs) of SC, which are indices of sympathetic nervous system activity. Because studies assess these physiological measures during both baseline (autonomic activity in the absence of external stimuli) and as a response to experimental stimuli (Lorber, 2004), we included both baseline measures or measures assessed in the context of a task (e.g. picture viewing, startle paradigm, attention-based tasks). According to a recent review of the literature, we expect deficits among youth high on CP to be more evident in measures of SC than HR or HRV (Fanti, 2018). Further, we expect to identify reduced sympathetic and parasympathetic cardiac activity among those at risk for CP, suggesting under-arousal and co-inhibition of both nervous systems. Since there was no meta-analysis testing these associations in the last decade, findings are expected to advance existing work aiming to understand the association between CP with physiological baseline activity and task-related reactivity.

2. Method

We followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al., 2009). The protocol of this systematic review was registered in PROSPERO (CRD42018092305) (Fanti et al., 2018a). Data were extracted from the published reports (journal article) of the studies or obtained from study authors. The PRISMA checklist is reported in the Supplemental Material 1.

2.1. Types of studies

Two types of studies were included: 1) Case-control studies comparing any of the outcomes of interest in subjects with conduct disorder/oppositional defiant disorder problems and healthy comparisons without conduct disorder/conduct problems; 2) Correlational studies assessing the correlation between severity of CP and any of the outcomes of interest.

2.2. Types of participants

We included studies assessing children and/or adolescents (aged ≤ 18 years): 1) with conduct disorder, defined based on the DSM (any version) criteria; or 2) in which conduct problems was measured by means of a validated scale, completed by parents, teachers, or self-reported by the child/adolescent, as listed in the INSERM collective report on Conduct Disorder in children and adolescents (INSERM Collective Expertise Centre, 2005): Broad-spectrum interviews: K-SADS (Orvaschel and Puig-Antich, 1987), ISC (Kovacs, 1985), DISC-IV (Shaffer et al., 2000), CSI (Gadow and Sprafkin, 2002); Behaviour scales: CBCL (Achenbach and Edelbrock, 1983), CTRS (Conners, 1969), CPRS (Conners, 1997), ECBI (Eyberg et al., 1980), HSQ/SSQ (Barkley, 1981), SESBI-R (Eyberg and Pincus, 1999), SBQ (Clark, 1995); Aggression scales: OAS (Silver and Yudofsky, 1991), BDHI (Boone and Flint, 1988), DIAS (Björkqvist et al., 1992), CSBS/CSBT (Crick, 1996; Crick and Grotpeter, 1995).

2.3. Outcomes

Primary outcomes included: 1) any measure of heart activity/reactivity, including heart rate (HR), heart rate variability (HRV), pre-ejection period (PEP) or Respiratory Sinus Arrythmia (RSA); 2) any measure of skin conductance, including galvanic skin reactivity parameters such as skin conductance level (SCL) or skin conductance response (SCR). Both parameters measured in the context of performing a task (e.g., picture viewing, startle paradigm, attention-based tasks) or taken as baseline measures were included (rest, activity and reactivity outcomes).

2.4. Search strategy/syntax

The following electronic databases were searched until February 13th, 2018, with no language/date/type of document restrictions: Pubmed (Medline), Ovid databases (PsycInfo, Embase + Embase classic, Ovid Medline), and Web of Knowledge databases [Web of science (Science Citation Index Expanded), Biological abstracts, Biosis, Food science and technology abstracts]. Additional details on the search strategy/syntax, including search terms for each database, are reported in the Supplemental Material 2. References of included studies were hand-searched to find additional pertinent studies not detected with the electronic search.

2.5. Study selection

Retrieved references were independently screened and blindly double-coded for eligibility by two study authors. Any disagreement was resolved by a senior author. If needed, study authors were contacted to gather missing/additional information to clarify study inclusion.

2.6. Data extraction and statistical analysis

Data extraction was performed blindly by two of the authors, and any discrepancy between the two was resolved by consensus with a third senior author. We contacted study authors when necessary. Data extracted from each study included: 1) Publication details: year and language of publication; 2). Design: type of study (cross-sectional, case-control, cohort, correlational, etc.); study temporality (prospective, retrospective); patient enrolment (consecutive, non-consecutive); setting (clinical, general population vs epidemiological population study); 3) Study participant details: number, mean age (SD), sex distribution, Socioeconomic status (SES) and ethnicity of participants with and without CP or conduct disorder; characteristics of participants without conduct problems/disorder (healthy comparisons, other); psychiatric comorbidities of individuals with and without conduct problems/disorder (type and prevalence); method to establish the diagnosis of conduct problems/disorder (self-reported symptoms/diagnosis, diagnosis recorded in medical files/registry, structured or semi-structured interview according to clinical criteria); 4) Outcome measures: method used to define conduct problems/disorder (self-reported diagnosis, diagnosis in medical file/registry); prevalence (unadjusted and, if reported, adjusted) of conduct problems/disorder; method used to measure psychophysiological parameters; data reduction methods; tasks or paradigms used in the study. Age of onset was dropped as a variable of interest based on the low number of studies differentiating or reporting age of onset.

We included measures of baseline heart activity (HR, RSA, PEP, HRV) as well as measures of heart reactivity. In addition, we included baseline and reactivity measures of skin conductance (SCL and SCR). Contrary to the pre-registered methods and in response to reviewer suggestions, we decided to include all available physiological data from each study, without prioritizing specific physiological outcome measures in order to be more inclusive. However, we adhered to the following hierarchy in extracting and analyzing data when several options for given outcome measures were available:

Changes between baseline and activity during tasks were preferred to reactivity during task data, which in turn were preferred to baseline only data. Although we were interested in both baseline and task-related measures, we prioritize task related over baseline data because prior work provided evidence that task related measures have a greater influence on CP (see Fanti, 2018 for a review). If different types of emotional stimuli were available, preference was given to aversive tasks (e.g., fearful faces, baby crying) due to their relevance to the stress and threat system that relates to antisocial behaviors.

For mixed sample reports we included mixed sample data, and for studies reporting sex differences, we meta-analytically combined data on the two samples divided by sex. If only female or only male data were reported, we used the ones that were available.

In case of several measurement points, we used the one for which both, physiological and behavior/CP data, were reported. If both were reported for several assessment points, we used the earliest time point.

We extracted means and standard deviations for group-based results as well as zero-order correlations for correlational results. Furthermore, we extracted reactivity measures based on which types were provided. If delta scores were provided, those were included; if baseline and task data were provided, we use the measures during the task that were provided.

Random-effect models were used to compute pooled effect size for each outcome. For case-control studies, we calculated the standardized mean difference (SMD), with 95% confidence interval (CI), with the correction of Hedges (Hedges, 1981) to avoid bias due to sample size. The pooled SMD, and related 95% CI, or correlation coefficients were calculated through the inverse variance method, and its statistical significance was assessed by the Z statistic. I^2 (Higgins and Thompson, 2002) was calculated to compare heterogeneity among studies. Finally, Egger's test (Egger et al., 1997) and funnel plots were used to evaluate publication bias. Analyses were performed using Comprehensive Meta-Analysis (https://www.meta-analysis.com/) software.

3. Results

3.1. Study selection process and study characteristics

The process of the study selection can be seen in Fig. 1. Details about the search can be found in Supplementary materials 3. From an initial pool of 2016 potentially relevant references, 66 studies were retained for the quantitative analyses. Supplemental Tables 1 and 2 show the 34 case-control and 32 correlational studies, respectively, included in the meta-analyses. Of those 34 case-control studies, five reported Baseline HR data, 18 task-related HR change data, two task-related HRV, six task-related RSA data and five task-related PEP data. Regarding skin conductance outcome measures, four reported Baseline outcomes (2 SCR and 2 SCL) and 19 reported task-related outcomes (nine SCR, 10 SCL). The 32 studies with correlational design included 14 studies with Baseline (eight HR, four RSA and 2 PEP) and 19 studies with task-related (6 HR, 10 RSA and 3 PEP) cardiovascular outcome measures, as well as eight studies with SCL outcome data, of which three with Baseline data and five with task-related data. Single studies could contribute to more than one outcome to the different meta-analyses.

3.2. Meta-analyses

Table 1 summarizes the results of the meta-analyses in relation to the planned outcomes (HR, RSA, HRV, PEP, SCL and SCR) and on baseline versus task reactivity. For the **case-control studies** we found a significant effect for task-related SCL (pooled *OR* = −0.862, 95% CI [−1.725; −0.227]), indicating significantly lower SCL reactivity in tasks in the CP groups compared to control groups. However, I^2 was rather high, indicating that 66% of the variance was due to true variation among studies, rather than sampling error, and the Egger's test indicated the possibility of publication bias (*p* = .012). Excluding one study with a substantially large effect size (OR = −5.962; Mangina et al., 2000) from the meta-analysis lead to a low I^2 (5.100), while the pooled effect size remained significant (pooled *OR* = −0.427, 95% CI [−0.679; −0.175]). The meta-analysis of case-control studies with SCR outcome measure in response to tasks also showed a significant effect (pooled *OR* = -0.364, 95% CI [−0.501; −0.227]), indicating a significantly lower SCR response to tasks in the CP groups compared to control groups. In this case, I^2 was low, indicating that variance was unlikely to be accounted for by study heterogeneity, but, rather, to sampling error, and Egger's test indicated low possibility of publication bias (*p* = .416). Furthermore, we found a significant effect for task-related RSA (pooled *OR* = −0.206, 95% CI [−0.398; −0.014]) with a low I^2, indicating low probability for a heterogeneity-based effect. The meta-analysis for task-related PEP showed a significant effect (pooled *OR* = 0.597, 95% CI [0.245; 0.948]), which could be based on
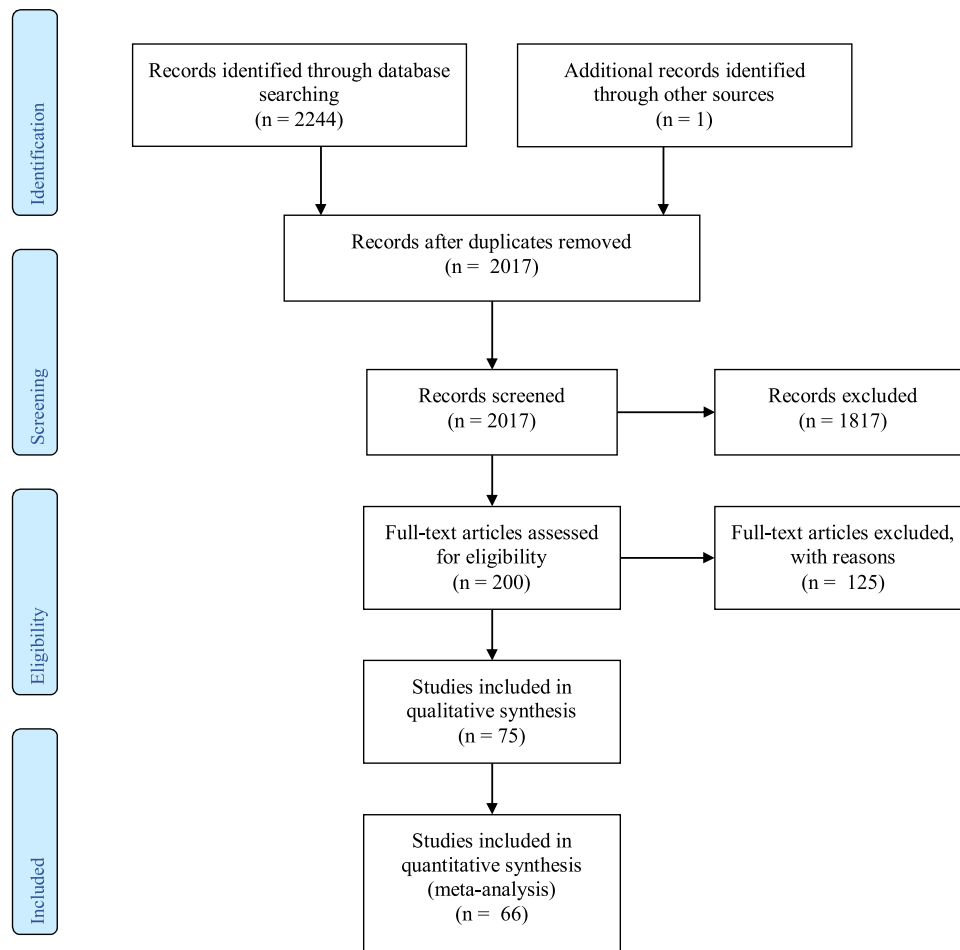
Fig. 1. Prisma chart for the study selection process.

heterogeneity, as I^2 was rather high. However, this might be due to the large effect of one study (Crowell et sl., 2006) with a standard difference of the means of 1.328 (95% CI [0.625;2.031]). Given that PEP reactivity is represented by shorter intervals (i.e., negative numbers), the identified positive effect indicate less PEP reactivity among those in the CP group (Brenner and Beauchaine, 2011). Meta analyses comparing CP and control groups for baseline or task related HR or HRV and for baseline SCR or SCL did not find any significant differences (see Table 1).

For the **correlational studies**, we found a significant effect for studies with HR baseline outcome measures (pooled correlation: -0.139, 95% CI [−0.227; −0.048]), indicating a lower baseline HR for individuals with higher CP symptom scores. Study heterogeneity was

Table 1
Meta-analytic results overview.

Design	Outcome variable	Number of studies	Meta analytic effect	CI	I^2
Case-Control	Baseline HR	5	−0.326	[−0.784; 0.132]	65.337
	Task-related HR	18	−0.155	[−0.415; 0.105]	80.055
	Task-related HRV	2	−0.300	[−0.654; 0.053]	0.000
	Baseline RSA	0			
	Task-related RSA	6	−0.206*	[−0.398; −0.014]	0.000
	Task-related PEP	5	0.597*	[0.245; 0.948]	55.245
	Baseline SCL	2	−0.188	[−0.763; 0.387]	57.479
	Task-related SCL	10	−0.862*	[−1.450; −0.274]	90.946
	Baseline SCR	2	−0.478	[−1.397;0.441]	76.690
	Task-related SCR	9	−0.364*	[−0.501; -0.227]	0.000
Correlational	Baseline HR	8	−0.139*	[−0.227; −0.048]	79.714
	Task-related HR	7	−0.165*	[−0.265; -0.061]	64.805
	Baseline RSA	4	−0.060	[−0.132; 0.013]	0.000
	Task related RSA	11	0.004	[−0.044; 0.051]	0.000
	Baseline PEP	2	−0.020	[−0.115; 0.077]	0.000
	Task PEP	3	−0.056	[−0.270; 0.164]	67.675
	Baseline SCL	3	0.049	[−0.058; 0.154]	40.452
	Task-related SCL	7	0.023	[−0.122; 0.167]	74.255
	Baseline SCR	0			
	Task-related SCR	0			

Note: * = significant meta analytic effect, I^2 = Information criterion.

Table 2
Subgroup Meta-analyses overview.

Design	Outcome variable	Number of studies	Subgroup	Meta analytic effect	CI	I^2
Correlational	Task-related HR	2	Boys	0.159*	[0.055; 0.259]	0.000
			Girls	−0.004	[−0.135; 0.127]	0.000
Case-control	Task-related HR	3	ADHD +	−0.037	[−0.268; 0.194]	0.000
			ADHD-	0.080	[−0.420; 0.580]	73.887
	Task-related SCR	3	ADHD +	−0.538*	[−0.937; −0.138]	64.773
			ADHD-	−0.375*	[−0.697; -0.053]	27.666
	Task-related HR	2	CU +	−0.109	[−0.492; 0.274]	0.000
			CU-	−0.136	[−0.609; 0.336]	33.514

high in this meta-analysis (79%); Egger's test indicated low possibility of publication bias ($p = .099$). We also found a significant effect for task-related HR (pooled correlation: −0.165, 95% CI [−0.265; −0.061]), pointing to lower task related HR among those high on CP. Again, high study heterogeneity (65%), and a low probability for publication bias ($p = .476$) was identified. Studies including baseline and task-related RSA or PEP as well as baseline and task-related SCL did not provide any significant pooled correlations (see Table 1).

3.3. Subgroup meta-analyses

For studies including subgroups, we ran additional meta-analyses independently for each subgroup if there was more than one study per outcome measure. From studies with correlational design, two reported subgroups data regarding sex. A meta-analysis restricted to boys across those two studies showed a significant effect (pooled correlation: 0.159, CI [0.055; 0.259]), indicating a positive correlation between CP measures and task-related HR increase, with a low heterogeneity score (< 0.001%). As this includes only two studies, no Egger's test could be calculated. The analysis restricted to girls however did not find a significant effect. From studies with case-control design, three reported task-related HR changes for participants with CP and ADHD: there was no significant pooled OR for either groups with ADHD (ADHD+: pooled OR = −0.037, CI [−.268; 0.194]), nor groups without ADHD (ADHD-: pooled OR = 0.080, CI [−0.420; 0.580]). For three studies reporting task-related SCR, both subgroup meta-analyses for ADHD + and ADHD- groups found significant effects with lower task-related SCR for those with CP compared to control groups (ADHD +: pooled OR = -0.538; ADHD-: pooled OR = −0.375) For the ADHD + subgroup analysis, study heterogeneity was rather high (65%), whereas for the ADHD- subgroup study heterogeneity was low (28%). Two studies reported data for CP groups with and without CU traits for task-related HR. Both meta-analyses for CU + and CU- did not reveal any significant effect for groups (CU +: pooled OR = −0.109; CU-: pooled OR = −0.136).

Finally, we ran sub-group analyses for case-control (CC) studies, for clinical versus non-clinical sample studies, where we categorized clinical sample studies by group definitions using diagnostic thresholds for conduct disorder versus other measures. We computed these for all outcome measures with more than one study in each sub-group: CC HR Task: (12 clinical versus 6 non-clinical studies), CC RSA Task (2 clinical versus 2 non-clinical studies) and CC SCR Task (5 clinical versus 4 non-clinical studies). Results for each of the three outcomes did not differ between the subgroups. A meta-regression testing the difference between clinical and non-clinical samples confirmed this finding (pooled correlation: -0.065, 95% CI [-0.680; 0.551]; $Q(1) = 0.04$; $p = 0.837$) (see Supplementary material Figs. 17–31).

3.4. Study quality

Regarding case-control studies, the average score at the Newcastle Ottawa Scale (NOS) was 6.16 (SD = 1.33). As for correlational studies, the average score was 3.1 (SD = 5.3). Details for each study are reported in Supplemental Tables 3 and 4.

4. Discussion

We systematically reviewed published studies reporting autonomic nervous system activity (cardiovascular and skin conductance) in youth with CP and meta-analyzed the relationship between CP and autonomic baseline as well as task-related reactivity across 66 studies, including a total of 10,227 participants. Across 34 included case-control studies that were based on CP cut-off scores, we found a significant pooled effect for task related skin conductance level (SCL) and reactivity (SCR), indicating lower galvanic skin activity in response to tasks, but no significant group differences for HR or HRV nor for any baseline measures. We also identified reduced task-related RSA and PEP reactivity, pointing to co-inhibition of parasympathetic and sympathetic systems and under-arousal as a potential mechanism explaining engagement in CP behaviors. However, across 32 studies with correlational design we found only significant negative correlations between baseline and task-related HR with CP, but no significant relationship of any other physiological measures assessed during tasks nor baseline.

The identified association between baseline HR and CP agrees with a prior meta-analysis suggesting that low baseline HR assessed during childhood and adolescence is a biological marker of aggressive and antisocial behavior (Ortiz and Raine, 2004). In addition, emotion re-activity studies found a relationship with task-based HR, indicating that CP are associated with low autonomic arousal both at baseline and as a response to emotional cues. However, these findings were only identified for correlational studies and with a rather large heterogeneity score, but a low chance for publication bias. Although there was a trend towards similar relationships in the case-control studies, these were not significant and were also based on rather heterogeneous studies. The non-significant effects in the difference between baseline and task-related HR identified in case control studies could be related to the law of initial values, which has been reported to impact specifically baseline to task changes of cardiac parameters (Berntson et al., 1994a,b). The inconsistency in findings regarding baseline HR for correlational versus case-control studies was also reported in a recent review of the literature, with studies showing no association or that CP are associated with low or high baseline and HR reactivity (Fanti, 2018). Thus, despite potential relevance of the study design, based on our meta-analysis and prior review of the literature, we cannot confirm a reduced HR activity for youth with CP. In addition, baseline levels of SC were not associated with CP, suggesting that if anything, baseline levels of HR might be a better predictor of CP compared to SC. However, only seven of the identified studies included baseline SC.

An important finding in case control studies assessing cardiac measures was that individuals high on CP exhibited reduced PEP and RSA reactivity. As a result, both correlational and case-control studies suggest that CP relate to autonomic hypo-arousal and hypo-reactivity towards challenging stressors. Findings are in line with previous suggestions of greater RSA withdrawal, associated with lower RSA reactivity, and lengthening of the PEP, associated with reduced sympathetic nervous system activity, as indicators of physiological under-arousal (Murray-Close et al., 2018). Although the HR effects identified in correlational studies cannot be attributed to a specific autonomic

system, RSA and PEP findings point to co-inhibition of sympathetic and parasympathetic systems that relates to low stress responsivity and fearlessness (Thomson et al., 2018). Low stress sensitivity and lack of fear might increase the likelihood to engage in high risk antisocial and CP behaviors.

Furthermore, the lower SC reactivity identified in case-control studies also suggest reduced sympathetic reactivity among those high on CP. These results have to be interpreted carefully. Across the different studies assessing SCL there was a very large heterogeneity and a higher potential for a publication bias, while the effect for the SCR based studies can be considered more substantial due to a very low heterogeneity and low possibility of publication bias. However, after excluding one study with a very large effect size that used a working memory task (Mangina et al., 2000) heterogeneity was reduced substantially, while the overall effect of lower SCL during tasks for those with CP remained. Interestingly, the task-based SC levels were not related to dimensional approaches of measuring CP in the correlational studies and there were no studies included in the analyses that reported skin conductance reactivity. In contrast to correlational studies that mainly used social stress tasks, the case-control studies relied on a variety of different tasks including physical, social performance, stress or fear conditioning. However, there was no task related pattern in the case-control studies that could explain the null finding identified in correlational studies.

Nevertheless, the findings provide greater support for SC compared to HR reactivity in understanding CP at the level of group comparison, which might involve more clinical populations. Indeed, the majority of prior work suggests that SC reactivity during emotional tasks is lower among youth high on CP compared to controls, which was not true for HR reactivity (Fanti, 2018; Lorber, 2004). A direct comparison of clinical versus non-clinical samples within the group comparison studies did not reveal any differences though, pointing potentially to differences based on extreme group rather than clinical versus non-clinical types of samples. Similar to a prior meta-analysis (Lorber, 2004), heterogeneity in effect sizes for HR reactivity ranged from negative to positive, suggesting considerable heterogeneity in effect sizes. The heterogeneity of effect sizes across studies might also be related to high inter-individual differences in HR and heart rate reactivity, especially in children, which has been discussed in the fitness assessment literature as well (Oliveira et al., 2017; Brooke et al., 2014).

Regarding the analyses taking individual differences and co-occurring psychopathology into account, we were only able to run subgroup analyses for comorbid ADHD, CU traits and sex. No studies met inclusion criteria to test differences in relation to internalizing co-occurrence. This is unfortunate, since it has been suggested that co-occurring internalizing symptomatology can explain heterogeneity in CP (Fanti and Kimonis, 2017). As a result, subgroup meta-analyses were not possible to the extent intended.

Our results for comorbid ADHD subgroups could be affected by the selection criteria: we excluded four correlational studies because they were using ADHD as main diagnostic criterion for CP (El-Sheikh and Hinnant, 2011; Keller and El-Sheikh, 2009; Prätzlich et al., 2018), while no case-control studies had to be excluded for this reason. At the same time, across the different correlational studies, the majority of them did not report ever screening for ADHD, so it was not possible to determine any subgroup analyses, while the majority of case-control studies screened for ADHD criteria. Still, we found that comorbid ADHD did not change the main findings regarding the relationship between task-related SCR and SCL being reduced in youth with CP in case-control-design studies. Similarly, no effect for task-related HR was identified after taking ADHD symptoms into account. Based on these findings, we can conclude that co-occurrence with ADHD symptoms does not influence the low SC reactivity identified among CP youth. Thus, the core physiological underpinnings associated with antisocial behavior might be similar in the two CP subgroups. Several studies reported that children with CP irrespective of ADHD symptoms show lower autonomic SC responses to aversive emotional stimuli, and interestingly both CP subgroups differed from healthy controls or youth with ADHD

symptoms alone (Herpertz et al., 2003, 2001; Northover et al., 2016; Zahn and Kruesi, 1993). This finding is noteworthy and suggests heterogeneity within ADHD symptoms when it comes to autonomic functioning, but not within CP.

Similarly, we found no difference for groups with or without comorbid CU traits for task-related HR and conduct problems. This is not in line with suggestions from the literature (see Frick et al., 2014b for a review), but only two studies met inclusion criteria in the present meta-analyses pointing to contradicting evidence (Anastassiou-Hadjicharalambous and Warden, 2008; de Wied et al., 2012): Anastassiou-Hadjicharalambous and Warden (2008) found that children with combined CP and CU traits showed less HR change in response to an emotion evoking film (i.e., associated with fear) compared to both CP-only and control groups. In contrast, de Wied et al. (2012) found no group differences in response to angry films. Based on our data extraction decision, we did not include a finding from the latter study, which suggested that sad film stimulation provoked significantly lower reactivity in the CD + CU group compared to the CD-only and control groups. However, exploratory analysis that used the data from the sad movie condition did not change the overall results. As a result, no clear conclusions can be drawn based on existing findings. Additional work comparing CP-only with CP + CU groups is therefore needed, especially since this distinction has clinical importance due to the inclusion of a CU specifier to the DSM-5 diagnosis of conduct disorder (American Psychiatric Association, 2013).

The only two studies (Crozier et al., 2008; Eisenberg et al., 1996) that reported results separately for boys and girls suggested that higher task-related HR reaction was related to boys CP, but not girls. Unfortunately, no other studies reported related data, which would be important in order to investigate sex differences in physiological reactivity (see e.g. Prätzlich et al., 2018). This finding contradicts prior work suggesting that girls exhibit greater autonomic activity than boys (Beauchaine et al., 2008). In the case of the latter publication, our inclusion criteria did not allow to accommodate studies that created groups of youth based on latent class analyses. However, all studies reporting HR monitored during a task, included mixed samples of boys and girls and showed a trend for reduced HR reaction to tasks, although the pooled effect was not significant. Interestingly, Crozier et al. (2008) and Eisenberg et al. (1996) are the only studies that show a positive correlation in the main analysis. In these two studies, boys seem to drive the effect in terms of higher heart rate reactivity during task for those higher on CP, while there was no significant correlation for girls. The resulting high diversity of the studies in the main analysis reflects the differences between studies, which could be based on the diversity in the tasks, with a Trier Social Stress Test, Social Performance Paradigm or Social Stress Task on the side of the studies identifying negative correlations (Choy et al., 2015; Hastings et al., 2011, 2007; Portnoy et al., 2014) and an imagination task or watching crying babies films task on the side of the studies identifying positive correlations (Crozier et al., 2008; Eisenberg et al., 2012). This could point to a differentiation between (social) stress inducing situations compared to empathy evoking tasks. Eisenberg et al. (2012) argue that their finding might be due to the lower baseline in their data, while Crozier et al. (2008) argue that they found an increase in HR directly after the provocation was presented, but a decrease immediately prior to the provocation and therefore there might be different processes involved in each condition. Considering empathy provoking (other-related) situations to be significantly different from the more stress inducing tasks, they seem to lead to higher heart rate reactions in boys with conduct problems, while stress provoking (self-related) situations provoke less heart rate reactions with increased conduct problems.

4.1. Limitations

This systematic review and meta-analysis has some limitations: despite a large amount of studies reporting psychophysiological data in relationship to conduct problems (n = 75), only a smaller subset of 66 studies could be included due to non-reported data and difficulties

obtaining respective data from authors. This points to an urgent need for a more complete and open reporting in the field. Furthermore, we had to exclude several studies based on them reporting types of outcome measures that were unique in our reviewed studies sample (e.g., blood pressure or SCR for a correlational design) and therefore could not be pooled with other similar measures from any other study retained in our meta-analysis. These are limitations that come with reviewing psychophysiological data, which can be very diverse in terms of specific outcome measures and reported data type. In addition, as we had to create a set of hierarchies for the inclusion criteria for measurement types and for task type (if there were several ones), we could have introduced a selection bias. Although heterogeneity in experimental stimuli might contribute to the contradicting findings identified in physiological studies, Lorber (2004) suggested that taking the valence of the experimental stimuli into account might resolve some of these inconsistencies. In the present meta-analysis, we mostly focused on negative valenced stimuli following this suggestion, and, as discussed above, our descriptive comparison of tasks and stimuli used in the included studies showed no pattern based on the type of stimuli or tasks, but rather consistent effects across different types of stimuli and tasks. Finally, the assessment with the NOS suggested that most of the items were correctly addressed in the majority of the studies.

4.2. Future directions and conclusions

There are several important conclusions derived from this meta-analysis that can inform future work. First, SC reactivity might be an important biomarker for identifying youth high on CP, irrespective of ADHD comorbidity. Thus, the sympathetic nervous system, which is responsible for the "fight or flight" response, is a good candidate for explaining youth antisocial behavior. Lower responsiveness and stress reactivity to threatening stimuli, as indicated by the identified lower SC response, among children with CP might drive their engagement in antisocial behaviors, without considering the negative consequences associated with these behaviors (Fanti, 2018; Fanti et al., 2018a,b). Thus, the assessment of SC reactivity should be a research priority among studies interested in physiological measures that tap into stress or emotions. Based on evidence that baseline and task-related HR were identified as predictors of CP in correlational studies, we might be able to conclude that these physiological measures should also be used in empirical studies interested in the prediction of CP. HR was found to be an important measure for the identification of at risk children and the prediction of developmental stability in antisocial behavior (Fanti, 2019; Raine, 2015; Raine et al., 1997). Future longitudinal work might consider assessing baseline and task-related HR as well as SC reactivity as part of an etiological model to explain the development of stable and severe CP (Table 2).

Interestingly, although we did not identify an effect of HRV, co-inhibition of sympathetic (PEP) and parasympathetic (RSA) systems, was associated with CP. The majority of prior work fail to assess both sympathetic and parasympathetic autonomic activity, which might result in an incomplete picture of physiological deficits, especially since physiological systems work dynamically (Fanti, 2019; Porges, 2001; Thomson et al., 2018). Investigating the interaction between parasympathetic and sympathetic activity in response to emotional stimuli can provide a more complete picture of emotion dysregulation deficits (see Thomson et al., 2018 for an example). Moreover, there is a need to move beyond the single biomarker approach to better understand the impact of physiological stress response systems on antisocial behavior (Buss et al., 2018; Fanti et al., 2018b). Emotional experiences involve coordinated changes in the activity of various physiological systems, and variations in distinct physiological systems might provide evidence to explain prior contradicting findings. Current findings provide support for co-inhibition of sympathetic, as indicated by both SC and PEP measures, and parasympathetic, in accordance with RSA, systems pointing to decreased sympathetic and parasympathetic activity. This

finding agrees with work suggesting that co-inhibition puts children at risk for conduct problems by making them more vulnerable to stressful environmental experiences (El-Sheikh et al., 2009). Thus, it is important for future work to investigate multisystemic physiological responses to aversive stimuli in order to identify vulnerability factors associated with the expression of CP or other forms of psychopathology.

Another important message derived from the present meta-analyses is that correlational and case-control studies can result in different findings, and future empirical work should consider this information during study design. Furthermore, there is great variability in the experimental tasks used in physiological research. The use of standardized tasks to understand physiological reactivity might help to advance this line of work. Importantly, experimental tasks used in physiological work might not represent ecologically valid assessments, and future work might consider incorporating novel techniques, such as virtual reality tasks.

Finally, despite the complexity of existing work, the present meta-analysis was able to derive several conclusions that have the potential to inform biological vulnerability models. In fact, current findings can inform efforts towards research domain criteria and can be used as a basis for the design of novel biologically driven interventions. Based on the findings, the effectiveness of interventions designed for children and adolescents high on CP might increase if they focus on stress reactivity deficits as indicated by the co-inhibition in both sympathetic and parasympathetic autonomic systems. The assessment of both clinical and physiological outcomes can inform the mechanisms underlying treatment effects, and can advance the current state of the art.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2019.02.016.

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