Neurobiological Correlates of Aggression and Emotion Regulation in Children and Adolescents

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Content

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Abstract

Aggressive and antisocial behaviour is associated with impaired emotion regulation and neurobiological alterations that are reflected on the level of autonomic as well as central nervous system functioning. Recent research on central autonomic control – as posited in the neurovisceral integration model – indicates associations between autonomic nervous system (ANS) activity and functional and structural brain correlates. An overlap of the central autonomic network (CAN) with brain regions involved in emotion regulation highlights the relevance of ANS measures in research on emotion regulation and aggression.

The main aim of this thesis was to investigate and gain more insight into neurobiological correlates of aggression and emotion regulation in children and adolescents. First, we examined the relationship between resting ANS activity and aggression in more detail than has been done before. We therefore included a comprehensive assessment of ANS activity with two measures of general ANS activity (heart and respiration rate) and two measures capturing parasympathetic nervous system (heart rate variability) and sympathetic nervous system (pre-ejection period) activity separately, while considering relevant covariates such as smoking. A further sub aim was to gain more clarity on the best approach for linking psychopathology and neurobiology. Recent findings on a general psychopathology factor suggest that a dimensional approach captures psychopathology better than a categorical approach. Thus, we chose to compare two analysis approaches: a categorical (chapter 2) – based on DSM-5 – and a dimensional approach (chapter 3). The second aim of the thesis was to investigate functional brain correlates of implicit-controlled emotion regulation in individuals with and without conduct disorder (CD) (chapter 4). The third aim of the thesis was to investigate the relationship between resting heart rate variability and brain structure in female CD patients compared to typically developing adolescents (chapter 5).

The findings presented in this dissertation advance the knowledge on the neurobiology of aggression and emotion regulation in children and adolescents. In line with recent evidence, the presented studies suggest that resting ANS activity, especially heart rate, might not be as strongly correlated with antisocial behaviour as previously assumed. In addition, the novel finding of higher respiration rate in female CD suggests that this measure should be further considered in future research – with a particular focus on its potential to impact heart rate variability and emotion regulation. More research on respiration in aggressive individuals could improve current treatment modalities. Further, the result indicating that comorbid internalising disorders in female CD patients are associated with lower heart rate variability warrants additional investigation and consideration of specific treatment needs. This

CD group might represent a more severe psychopathological subgroup with more pronounced emotion regulation problems. Our findings of the neural correlates of implicit emotion regulation additionally support the notion of CD being characterised by deficient emotion regulation. Moreover, we reported negative correlations between resting heart rate variability and brain structure in CAN regions, which are implicated in emotion regulation. We highlighted the relevance of smoking for emotion regulation – which has been neglected so far in the context of neurobiological research on aggression and might be an important confounding factor to consider in future studies.

Chapter 1 General Introduction

1.1 Antisocial and Aggressive Behaviour

Antisocial and aggressive behaviour, comprising psychopathic tendencies and delinquent behavior, represent major public health and societal concerns (Portnoy & Farrington, 2015). Disruptive behavior disorders (DBD) represent around 40 to 60 % of the referrals of children and adolescents to mental health institutions (Steiner, Daniels, Stadler, & Kelly, 2017). The two main diagnoses under the umbrella term of DBD are conduct (CD) and oppositional defiant disorder (ODD). CD is a clinical manifestation of severe antisocial and aggressive behaviour and its diagnostic criteria include aggressive (e.g., fighting, bullying, vandalism) and rule-breaking behaviour in children and adolescents (e.g., lying, theft, truancy; (American Psychiatric Association, 2013)). The diagnosis of ODD designates a less severe form of conduct problems, characterised by angry and irritable mood, vindictiveness and defiant behaviour (American Psychiatric Association, 2013) and often precedes the development of CD (Moffitt et al., 2008). Male adolescents show higher prevalence rates of antisocial behaviour compared to female adolescents. These gender differences are evident as early as in 17 months old infants (Baillargeon et al., 2007). Recent evidence shows increasing prevalence rates for girls. Thus, research recognizes the need to consider this understudied group more systematically. Importantly, female adolescents with DBD might have different needs than their male counterparts, requiring specific treatment programme adaptations (Kersten et al., 2016). Due to the heterogeneity of antisocial and aggressive behaviour, a number of attempts have been made to characterise various subtypes or phenotypes, e.g., proactive/reactive aggression, conduct disorder with elevated psychopathic/callous-unemotional traits (CU), or in combination with internalising symptoms or previous traumatic experiences (Steiner et al., 2017). CU traits comprising a lack of empathy, reduced guilt or reduced affective responding have been identified as important subtyping characteristics of children and adolescents with antisocial behaviour, although CU traits can also occur in typically-developing children and adolescents (Fanti, Demetriou, & Kimonis, 2013; Herpers, Rommelse, Bons, Buitelaar, & Scheepers, 2012; Raschle, Menks, et al., 2017). In addition to the empathy deficits, three other neuro-cognitive core mechanisms have been identified to be dysfunctional in adolescents with conduct problems: acute threat response, reinforcement-based decision-making, response inhibition (Blair, Veroude, & Buitelaar, 2016). Response inhibition, as an executive function, is related to emotion regulation (Jiang, Li, Du, & Fan, 2016; Teper & Inzlicht, 2013) which is altered (Roberton, Daffern, & Bucks, 2012) and deficient in aggression (Davidson, Putnam, & Larson, 2000). CD (Cappadocia,

Desrocher, Pepler, & Schroeder, 2009) and especially ODD are associated with emotion dysregulation (Cavanagh, Quinn, Duncan, Graham, & Balbuena, 2017).

Figure 1 shows an overview of the topics covered in this thesis and illustrates the centrality of emotion regulation which connects antisocial and aggressive behavior with neurobiological functioning on different levels of analysis. In the following sections a detailed description of this connection will be presented. The section begins with the definition of emotion regulation and the categorisation of its strategies. Subsequently, the neural correlates of emotion regulation and aggression are described. In the following section autonomic correlates of aggressive behaviour are introduced. Further, the central autonomic control and its relationship to emotion regulation and aggression will be highlighted using the neurovisceral integration model (Thayer & Lane, 2000, 2009). Finally, the gaps in the literature and the aims of the thesis are summarised in the end of the section.

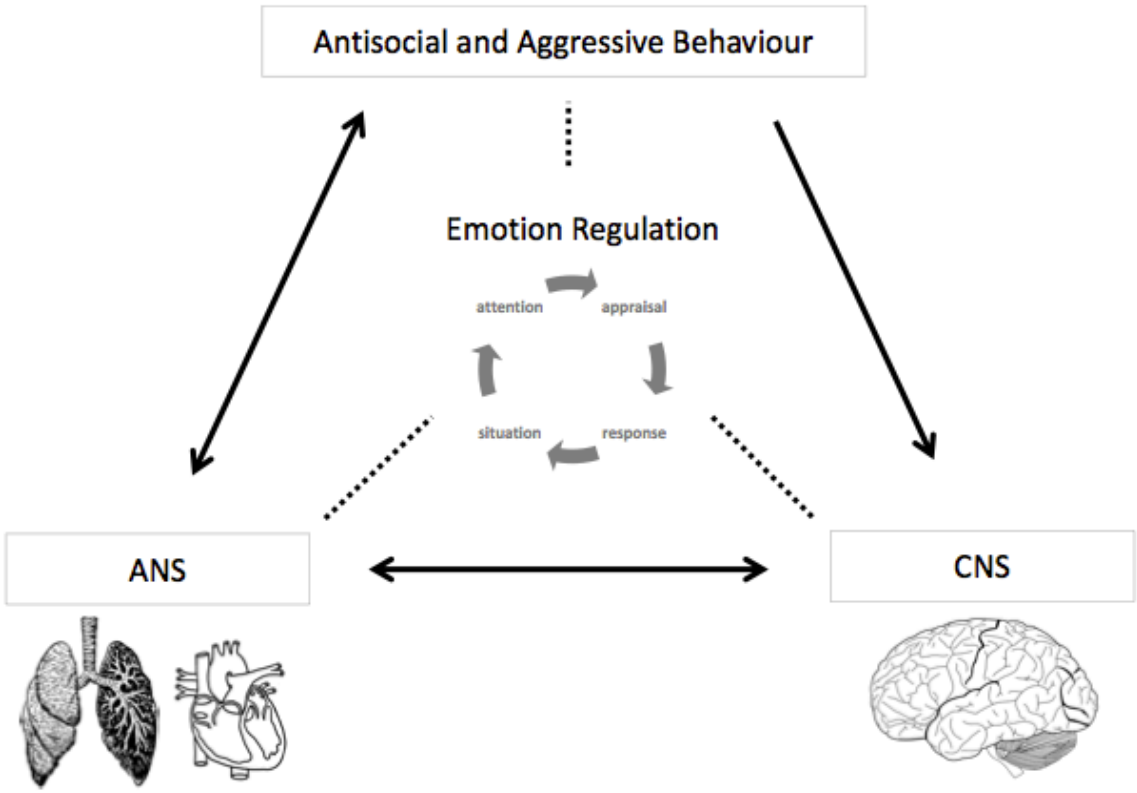

Figure 1. Overview of topics covered in this thesis. ANS = autonomic nervous system; CNS = central nervous system.

1.2 Emotion Regulation

1.2.1 Definition and Categorisation

The ability to regulate emotions enables an individual to adapt appropriately to continuously changing inner and outer circumstances and is crucial for the health and well-being of oneself and others (DeSteno, Gross, & Kubzansky, 2013; Ekman, 2003). Emotions can be considered as a driving force of our behaviours as they prepare us to act in a certain way. As such the ability to regulate them "determines" in which behaviours we engage or not. If for instance, someone gets in our way, hinders us in achieving our goal – which is a general trigger of anger – the behavioural tendency is to remove the obstacle, either physically or verbally. If we were not able to regulate this particular emotion we would constantly get into trouble with our fellow men, having problems finding a job, maintaining relationships and so on. A particular danger of anger is that it can be infectious, elicit anger in other individuals and can quickly lead to escalation (Ekman, 2003). Persistent unregulated or dysregulated emotions can eventually lead to psychopathology. In the case of anger it can lead to aggression which is associated with several psychiatric conditions (Blair, 2012), such as CD and ODD (Blair et al., 2016). It is important to note that anger is not the only emotion involved in aggression. Generally speaking, maladaptive regulation of emotions, such as expressive suppression, might lead to negative consequences, such as cognitive resource depletion (Friese, Binder, Luechinger, Boesiger, & Rasch, 2013; Richards & Gross, 2000). This might obstruct the ability to engage in more constructive emotion regulation strategies and enhance aggressive behavioural tendencies (Roberton et al., 2012).

The definition of emotion regulation includes the alteration of "the nature, magnitude, and duration of our emotional responses" (Ochsner, Silvers, & Buhle, 2012). Emotion regulation strategies can be categorised according to the process model of emotion regulation (Gross & Jazaieri, 2014). As this model is based on the modal model of emotion generation (Fig 1, centre), it allows to illustrate in which stage of this process the emotion regulation strategy is located. Five main categories of emotion regulation strategies are derived from this model: situation selection, situation modification, attentional deployment, cognitive change, and response modulation. Situation selection refers to choosing a certain situation, approaching or avoiding it in order to influence the anticipated emotion. When an individual is in a specific situation, situation modification allows an individual to adapt the circumstances to regulate an emotion. Attentional deployment relies on our ability to direct the focus of our attention on different aspects of a situation, positive or negative aspects of a given situation, depending on the goal, increasing or decreasing an emotion. Distracting oneself would be an example of this type of strategy. Cognitive change is one of the most studied emotion regulation strategies

(Ochsner et al., 2012) and aims to alter the appraisal of a situation, to change how one thinks of a certain situation. The last strategy response modulation aims at influencing, dampening or enhancing the emotional response, for instance through expressive suppression.

A recent framework (Braunstein, Gross, & Ochsner, 2017), which is complementary to the process model of emotion regulation, organises emotion regulation strategies on two orthogonal dimensions: goals and processes of emotion regulation. The goals range from explicit to implicit, which means that an individual consciously or unconsciously maintains an emotion regulation goal, whereas the processes to achieve this goal can range from controlled to automatic. Thus, the combinations included in this framework lead to four classes of emotion regulation strategies. The bulk of knowledge acquired in this research field is about explicit-controlled emotion regulation which includes for instance selective attention, distraction and reappraisal. Implicit-controlled emotion regulation can arise as a side-effect of cognitive control resources used for another task (Braunstein et al., 2017). This class encompasses tasks examining executive functions such as interference control, sustained attention or response inhibition with an emotional component included, such as in the emotional/affective Stroop (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006; Euler, Sterzer, & Stadler, 2014; Raschle, Fehlbaum, et al., 2017) or emotional go/no-go paradigm (Casey et al., 2011; Hare et al., 2008). The interaction of cognitive and affective systems plays a crucial role for the regulation of emotions (Ochsner et al., 2012). Diverse neuropsychological tasks can be applied to assess these systems, either separately or in conjunction, such as in the above mentioned tasks measuring inhibitory control combined with an affective component. The reduced ability to control or inhibit behavioural responses is associated with aggressive, impulsive behaviour and substance abuse (Blair et al., 2016).

In this thesis, the focus is on implicit-controlled emotion regulation. This strategy, involving controlled change processes, might offer insights which could potentially support the development and refinement of treatment approaches. It is particularly promising in this regard, as evidence has been shown that these processes are trainable (Chiesa, Calati, & Serretti, 2011; Tang, Tang, & Posner, 2016; Wheeler, Arnkoff, & Glass, 2017).

1.2.2 Neural Correlates

Emotion regulation can be measured on a subjective, behavioural as well as on a biological level. Numerous neuroimaging studies contributed to reveal the brains network involved in emotion regulation. The above mentioned interplay between cognitive control and affective systems in order to modify emotional responses is reflected by fronto-limbic interactions (Ochsner et al., 2012). Accordingly, the functional and structural connectivity between limbic structures, such as the

amygdala, and the prefrontal cortex has been related to emotion regulation skills (Lapate et al., 2016; Lee, Heller, Van Reekum, Nelson, & Davidson, 2012). Specifically, the inverse amygdala-prefrontal cortex connectivity was positively associated with reappraisal success of negative emotional stimuli (Lee et al., 2012). A disrupted fronto-limbic connectivity has been reported in a variety of psychiatric conditions, such as conduct disorder, anxiety (Lindner et al., 2018) and depression (Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015). Furthermore, a weaker functional connectivity was found as early as in 4 to 7 year old children and linked to increased aggression and attention problems (Park et al., 2018). The four following regions have been identified as control regions being most consistently activated in controlled emotion regulation based on a review (Ochsner et al., 2012) and several meta-analyses (Buhle et al., 2014; Diekhof, Geier, Falkai, & Gruber, 2011; Kohn et al., 2014; Morawetz, Bode, Derntl, & Heekeren, 2017): dorsolateral (dlPFC) and ventrolateral prefrontal cortex (vlPFC), dorsal anterior cingulate cortex (dACC), dorsal medial prefrontal cortex (dmPFC) and parietal region (Buhle et al., 2014). A conjunction analysis revealed consistent involvement of the left VLPFC, the anterior insula and the supplementary motor area across emotion regulation strategies (Morawetz et al., 2017). The affect regions which are assumed to be modified by the control regions while reappraising are located in the amygdala (Buhle et al., 2014) and ventral striatum (Kober et al., 2010). However, the activity of the bilateral amygdala was most consistently reduced, whereas no activity was found in other regions involved in emotional responses (Buhle et al., 2014). To date, only one study investigated implicit emotion regulation in adolescents with DBD (Hwang et al., 2016). The cognitive control region within the vmPFC together with the affective region of the amygdala exhibited reduced activity in response to negative emotional stimuli in the DBD group with a high level of CU traits compared to healthy adolescents and adolescents with DBD, but low in callous-unemotional traits. In addition, the DBD group showed a decreased insula response in trials with high cognitive load compared to the healthy group.

As mentioned above, aggression can be considered as deficient emotion regulation which reflects abnormalities in the underlying emotion regulation network of the brain (Davidson et al., 2000). Accordingly, brain regions involved in emotion regulation exhibit structural and functional alterations in adolescents with aggression (Raschle, Menks, Fehlbaum, Tshomba, & Stadler, 2015; Rogers & De Brito, 2016). Further evidence from experimental studies manipulating brain activity through stimulation highlight the importance of the PFC for the regulation of emotion and aggression. Aggression, which has been induced through social exclusion, has been reduced after stimulation of the rVLPFC with transcranial direct current stimulation (Riva, Romero Lauro, DeWall, Chester, & Bushman, 2014). Additionally, alcohol intoxicated individuals exhibited reduced activity in the mPFC

and dlPFC during aggressive acts, corroborating that PFC dysfunction figures prominently in aggression (Denson, Blundell, Schofield, Schira, & Krämer, 2018).

1.2.3 Autonomic Correlates

1.2.3.1 Basic Measures and Main Results in Aggression

The autonomic nervous system might offer additional access to the study of aggression and emotion regulation, since it is closely connected to the brain which is structurally and functionally altered in aggression. The main task of the ANS is the maintenance of homeostasis which requires adaptive reactions to the continuously changing inner and outer circumstances. Emotions signal a person when something of significance is happening and thus prepare behavioural tendencies. This preparation is accompanied by physiological changes such as in heart rate, respiration rate, sweating, blood pressure or skin temperature (Kreibig, 2010). The ANS innervates the organs needed for this adaption, such as the lungs and the heart, which are activated according to the metabolic demands of a specific situation. For instance, in a threatening situation, the organism activates the systems needed for handling the situation (e.g., cardiorespiratory system) while at the same time inhibiting the parts which are irrelevant for the situation (e.g., digestive system). This activation and inhibition occurs through two of the main branches of the ANS – the sympathetic (SNS) and the parasympathetic (PNS) part respectively. The SNS enables a fight-or-flight reaction and the PNS is associated with restorative body functions (Cannon, 1915). However, the ANS is able to generate more differentiated responses in order to facilitate adaptive reactions, since the SNS and PNS can be coactivated, coinhibited or reciprocally activated (Berntson, Cacioppo, & Quigley, 1991). The heart is dually innervated by both branches, thus its frequency reflects a mixed activity of the SNS and PNS. Most prominently, low resting heart rate has been confirmed as a robust physiological correlate of antisocial behaviour including, e.g., aggression, psychopathy and CD and ODD (Ortiz & Raine, 2004; Portnoy & Farrington, 2015). However, since higher PNS and/or lower SNS activity could result in low heart rate, it is not possible to distinguish which ANS branch is causing the low heart rate. Respiration is closely related to heart rate, as inhalation increases heart rate and exhalation decreases it, causing heart rate variability (HRV) or more specifically a phenomenon known as respiratory sinus arrhythmia. Respiratory sinus arrhythmia is caused by the PNS – as only this part of the ANS is fast enough to manifest those beat-to-beat changes in heart rate (Grossman & Taylor, 2007). Thus, HRV has been used as an indicator of cardiac PNS activity which has been negatively associated with aggressive and externalising behaviour (Beauchaine, Gatzke-Kopp, & Mead, 2007; Graziano & Derefinko, 2013) and emotion regulation difficulties (Williams et al., 2015). Moreover, it is proposed as a transdiagnostic biomarker of psychopathology and emotion

regulation (Beauchaine, 2015; Beauchaine & Thayer, 2015). To investigate the contribution of cardiac SNS activity, the pre-ejection period has been used and associated with reward processing which is affected in CD and ODD (Matthys, Vanderschuren, & Schutter, 2013; Sidlauskaite et al., 2017). Thereby, a lengthened resting pre-ejection period – indicating less cardiac SNS activity – was found in relation to conduct problems and aggression in children (Beauchaine et al., 2013). However, findings are not consistent throughout the literature. In contrast to lower ANS activity, some studies found no aberrant ANS activity, whereas others found even higher ANS activity in antisocial behavior (Calkins, Graziano, & Keane, 2007; de Wied, Boxtel, Posthumus, Goudena, & Matthys, 2009; Fagan, Zhang, & Gao, 2017; Posthumus, Böcker, Raaijmakers, Van Engeland, & Matthys, 2009; Schoorl, Van Rijn, De Wied, Van Goozen, & Swaab, 2016; Zahn-Waxler, Cole, Welsh, & Fox, 1995). These inconsistencies might reflect the heterogeneity of antisocial and aggressive behaviour, which has been described above. Especially two suptyping approaches resulted in distinct profiles of ANS acitivty: Internalising problems, which include depressive and anxiety symptoms, have been associated with autonomic over-arousal, whereas CU traits were more likely accompanied by autonomic under-arousal (Fanti, 2016). In the DSM-5, CU traits are included in the CD diagnosis as the limited prosocial emotions specifier (American Psychiatric Association, 2013). It has been shown that CU traits identify a more severe CD subtype, characterised by higher aggression, more CD symptoms and higher global impairment (Pardini, Stepp, Hipwell, Stouthamer-Loeber, & Loeber, 2012). Additionally, sex differences in ANS activity might contribute to some inconsistencies. Recent evidence suggest that gender differences in antisocial behaviour are mediated by a different resting heart rate (Choy, Raine, Venables, & Farrington, 2017). The higher heart rate in females throughout development is well documented (Koenig & Thayer, 2016; Nagy, Orvos, Bárdos, & Molnár, 2000; Ostchega, Porter, Hughes, Dillon, & Nwankwo, 2011). However, females are still underrepresented in studies investigating autonomic correlates of antisocial and aggressive behaviour (Ortiz & Raine, 2004; Portnoy & Farrington, 2015).

1.2.3.2 Central Autonomic Control

The term “autonomic” might suggest a greater degree of freedom from the central nervous system than actually exists (Langley, 1921). The central autonomic control has first been described in animal research (Benarroch, 1993; Saper, 2002) and is currently intensively investigated in humans (Beissner, Meissner, Bär, & Napadow, 2013; Ruiz Vargas, Sörös, Shoemaker, & Hachinski, 2016; Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012). This interplay of CNS and ANS supports the appropriate situational adaption of an individual. Neuronally, the central autonomic network (CAN: associated areas include the insula, amygdala, hypothalamus, brain stem and frontal brain regions) has been suggested to

regulate ANS activity (Benarroch, 1993; Saper, 2002). The regulatory role of the CAN was confirmed by several human neuroimaging meta-analyses (Beissner et al., 2013; Ruiz Vargas et al., 2016; Thayer et al., 2012). Thayer et al. (2012) selectively focused on the activity of the parasympathetic branch of the ANS, indexed by HRV combined with functional neuroimaging. The activity in the ventromedial prefrontal cortex and the amygdala were significantly associated with HRV. Beissner et al. (2013) followed a more comprehensive analysis approach including all studies relating brain activity to ANS outflow measures of the SNS and/or PNS. The amygdala, the insula and mid-cingulate cortices were identified as the core regions of the CAN. Further regulatory regions such as the ventromedial prefrontal cortex, mediodorsal thalamus, hippocampal formation, and hypothalamus were found. In addition to use HRV alone as a cardiac correlate of brain function, Ruiz Vargas et al. (2016) included heart rate in their analysis. The following brain regions were consistently associated with both cardiac measures: ventromedial prefrontal cortex, insula, precentral gyrus, amygdala, caudate, and medial frontal gyrus. Taken together, these studies established a correlational link between CAN areas and ANS activity. Recently – in an exploratory study – causal directed brain-heart interactions have been investigated using ultra-high field functional MRI combined with HRV assessment, which showed again a link between CAN areas and ANS outflow (Duggento et al., 2016). Another meta-analysis investigated the influence of non-invasive brain-stimulation (transcranial direct current stimulation and transcranial magnetic stimulation) on ANS functioning (Makovac, Thayer, & Ottaviani, 2017). The authors reported HR reduction and HRV increase after brain stimulation, with the largest effect after PFC stimulation compared to other areas, such as the motor cortex.

1.2.3.3 ANS and Brain Structure

Fewer studies investigated the link between resting ANS activity and brain structure. Woodward, Kaloupek, Schaer, Martinez, and Eliez (2008) showed a positive association between resting HRV and the cortical volume in the right ACC in combat veterans. This finding was not influenced by the presence of post-traumatic stress disorder. Winkelmann et al. (2016) found a positive correlation between resting HRV with cortical thickness in an area of the right anterior midcingulate cortex (aMCC) in healthy adults. In another study – including healthy adults – cortical thickness, especially in the left mPFC, was positively correlated with HRV and negatively with sympathetic nerve activity (Wood, Badrov, Speechley, & Shoemaker, 2017). Yoo et al. (2018) found significant correlations between HRV and cortical thickness in the left rostral ACC and the left lateral orbitofrontal cortex (OFC) in adults. Finally, Koenig et al. (2017) investigated structural brain correlates of resting heart rate and its variability in healthy female adolescents. In contrast to adult samples, a negative correlation between

HRV, but not heart rate, and cortical thickness of the bilateral rostral anterior cingulate cortex was found. Although, in one study a clinical sample was included, indicating no impact of the presence of emotional problems on the association between HRV and brain structure (Woodward et al., 2008), up to now no study has investigated the link between brain structure and ANS activity in aggression.

1.2.3.4 ANS and Emotion Regulation

The neurovisceral integration model (Thayer & Lane, 2000, 2009) emphasises the relationship between HRV and cognitive and emotion regulation processes. The model posits that HRV can indicate the activity of the neural network implicated in emotion regulation which overlaps, as described above, with the CAN (Thayer et al., 2012). For instance, it was shown that a higher HRV is associated with a better functional connectivity between the medial prefrontal cortex and the amygdala in adults (Sakaki et al., 2016). In contrast, this association was absent in individuals with post-traumatic stress disorder (Thome et al., 2017). Studies relating HRV to the neuropsychological correlates of self-regulation – measured amongst others with executive function or emotion regulation tasks – provide further evidence for the link between HRV and emotion regulation: Two recent meta-analyses confirmed a significant positive link between HRV and these tasks (Holzman & Bridgett, 2017; Zahn et al., 2016), although with a small effect of r=.15 and r=.09 respectively. Additionally, higher HRV was related with better performance on an emotion recognition task (Quintana, Guastella, Outhred, Hickie, & Kemp, 2012), associated with less self-reported difficulties in emotion regulation (Williams et al., 2015) and higher empathy as well as lower alexithymia (Lischke et al., 2018). Alexithymia has been associated with aggression and antisocial behaviour in clinical (Ates et al., 2009) and non-clinical (Fossati et al., 2009) populations, highlighting the importance of emotional awareness for emotion regulation (Gross & Jazaieri, 2014). Moreover, an experimental study manipulating the level of PNS activity was conducted to assess the relationship between HRV and emotional processes. Mechanical non-invasive carotid baroreceptor stimulation was applied, enhancing PNS outflow via the baroreflex, which decreased the activity within the left amygdala during the appraisal of fearful faces. Those individuals with lower HRV showed a stronger reaction to carotid stimulation indexed by a greater amygdala deactivation combined with lower self-reported fear intensity, compared to individuals with higher HRV (Makovac et al., 2015).

To conclude, these convergent lines of evidence, stemming from diverse sources of research, demonstrate a link between ANS activity, especially focused on PNS activity, and emotional processes, such as empathy, emotion recognition and regulation. Notably the overlap between central autonomic control and emotion regulation networks of the brain highlights the relevance of investigating ANS

activity in the context of emotion regulation, especially in the case of aggression where there is much evidence that emotion regulation and its neuronal underpinnings are impaired.

1.3 Gaps in the Literature and Aims of the Thesis

Overall, there is substantial evidence linking ANS markers to emotion regulation and different aspects of aggressive and antisocial behaviour (as illustrated in Fig. 1). However, the four ANS markers have rarely been included together in the same study. Furthermore, many previous studies had small sample sizes. In addition, numerous studies have highlighted the importance of including sex in the description of antisocial behaviour and ANS activity (e.g., Koenig & Thayer, 2016; Lehto-Salo, Närhi, Ahonen, & Marttunen, 2009), but only a small percentage of studies considered female participants (Ortiz & Raine, 2004; Portnoy & Farrington, 2015). The majority of studies on ANS activity and antisocial behaviour have not been controlled systematically for confounding factors that may differ between typically-developing and antisocial groups (Portnoy & Farrington, 2015) – even though smoking, sports, caffeine use, body mass index (BMI), medication use, IQ and socio-economic status have all been shown to influence ANS functioning and/or psychopathology (Alvares, Quintana, Hickie, & Guastella, 2016; Burke, Loeber, & Birmaher, 2002; Hu, Lamers, de Geus, & Penninx, 2017; Koenig et al., 2014; Martin et al., 2008; Piotrowska, Stride, Croft, & Rowe, 2015). In particular, the influence of smoking has only been examined in a few studies (Jennings, Piquero, & Farrington, 2013; Murray et al., 2016) – despite evidence indicating that smoking constitutes a risk factor for the development of antisocial behaviour and impacts brain and ANS functioning (Hu et al., 2017; Pagani, Lévesque-Seck, Archambault, & Janosz, 2017).

Thus, we aim to disentangle the role of different ANS parameters in female and male adolescents with antisocial and aggressive behaviour. We hereby aim to overcome several limitations of the previous literature by: including a comprehensive assessment of ANS activity with two general measures of ANS activity (heart rate and respiration rate) and two measures capturing PNS (heart rate variability) and SNS (pre-ejection period) activity separately. As respiration rate has only been investigated in animal research as a correlate of aggression, we also study the link between respiration rate and aggression. Moreover, we consider the influence of covariates such as smoking, sports, caffeine use, BMI, medication use, cardiac problems, IQ and socio-economic status.

An important reflection concerns the strategy to investigate the association between psychopathology and neurobiology. Traditionally, categorical diagnoses by way of classification systems such as the DSM are used to classify individuals. Subsequently, it can be investigated whether they differ in

neurobiological activity. However, the validity of the categorical diagnostic system has been questioned (Lilienfeld & Treadway, 2016). An alternative dimensional approach is the Research Domain Criteria (RDoC) framework developed by the National Institute of Mental Health. Shifting away from the categorical approach, RDoC aims at identifying core systems (biological, cognitive, social, positive/negative valence) that are impaired across psychopathology, examining the interaction of multiple biological systems as determinants of psychopathological vulnerability and identifying biological transdiagnostic constructs. The neurovisceral integration model aligns with RDoC (Beauchaine & Thayer, 2015). Recent findings on a general psychopathology factor suggest that a dimensional approach captures psychopathology better than a categorical approach (Caspi et al., 2014). Thus, we chose to compare two analysis approaches on the same sample (chapter 2 & 3).

In chapter 2 we set out to investigate our research aims in a categorical way – based on DSM-5 diagnoses – to compare individuals with and without conduct disorder. Further, we aim to investigate ANS patterns underlying different subgroups of CD females – based on DSM-5: CD with limited prosocial emotions (LPE) and CD with comorbid internalising disorders. In chapter 3 we follow a dimensional approach by investigating our research aims by analysing the sample as a whole, not separating between individuals with and without conduct disorder. Further, we aim to identify distinct physiological phenotypes and relate them to antisocial behaviour, which has not been done yet and accords with the RDoC approach.

Central autonomic control and emotion regulation share overlapping networks in the brain. Accordingly, ANS activity has been related to emotion regulation and to brain function in regions involved in emotion regulation. Adolescents with antisocial and aggressive behaviour exhibit functional and structural alterations in the emotion regulation network of the brain. However, the neural correlates of implicit-controlled emotion regulation are under-investigated in CD patients. Thus, in chapter 4 we aim to investigate the functional neural correlates of implicit-controlled emotion regulation using an affective Stroop task in CD patients compared to typically developing individuals. Additionally, emerging evidence shows associations between brain structure and resting ANS activity, with a particular focus on PNS activity, indexed by HRV. However, to date there is only one study with healthy female adolescents. Thus, in chapter 5 we aim to investigate correlations between brain structure and resting HRV in female adolescents with and without CD.

Chapter 2 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. The psychophysiological abnormalities observed in this subgroup are indicative of emotion regulation problems. Accordingly, this subgroup may require specific interventions.

Keywords: Conduct disorder, Psychophysiology, Autonomic nervous system, Sex differences, Emotion regulation

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) suggest 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.

Table 1 Demographic, Cognitive and Physical Characteristics of the Sample

General characteristics	FEMALE					MALE				
	CASE (N=296)		CONTROL (N=363)			CASE (N=187)		CONTROL (N=164)		
	M	*SD*	*M*	*SD*	t	*M*	*SD*	*M*	*SD*	t
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	-.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	-.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)

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 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 '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.

Table 2 DSM-5 Disorders in the Sample

	FEMALE		*MALE*	
	CASE (N=296)	*CONTROL* (N=363)	*CASE* (N=187)	*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 (.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)

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 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.

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 (N=296)		CONTROL (N=363)		CASE (N=187)		CONTROL (N=164)		Sex	Group	Sex x 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)

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 ($F(1,782) = 12.051$, $p < 0.01$, $\eta p2 = 0.015$)) and PEP ($F(1,600) = 19.429$, $p < 0.01$ ($\eta p2 = 0.031$)), 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 ($F(1,782) = 4.054$, $p < 0.05$, $\eta p2 = 0.005$). Post hoc tests revealed that female cases had a significantly higher RR than female controls ($F(1,539) = 5.256$, $p < 0.05$, $\eta p2 = 0.010$), whereas male cases and controls did not differ from each other ($F(1,239) = 0.876$, $p = .35$, $\eta p2 = 0.004$); see Fig. 1.

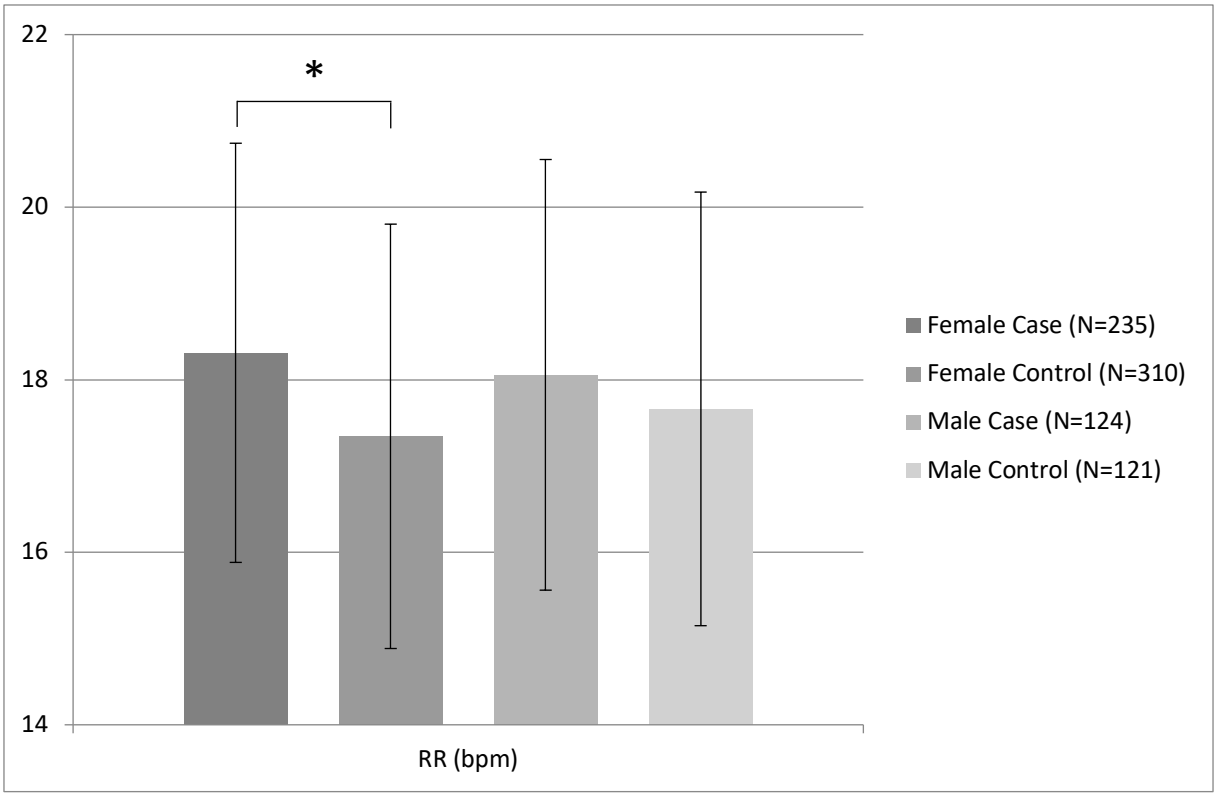

Fig. 1. Respiration Rate (RR) in beats per minute (bpm) in CD Females and Female Controls, CD Males and Male Controls.

Note. Error bars show standard deviations, and * indicates significance at the .05 level.

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.

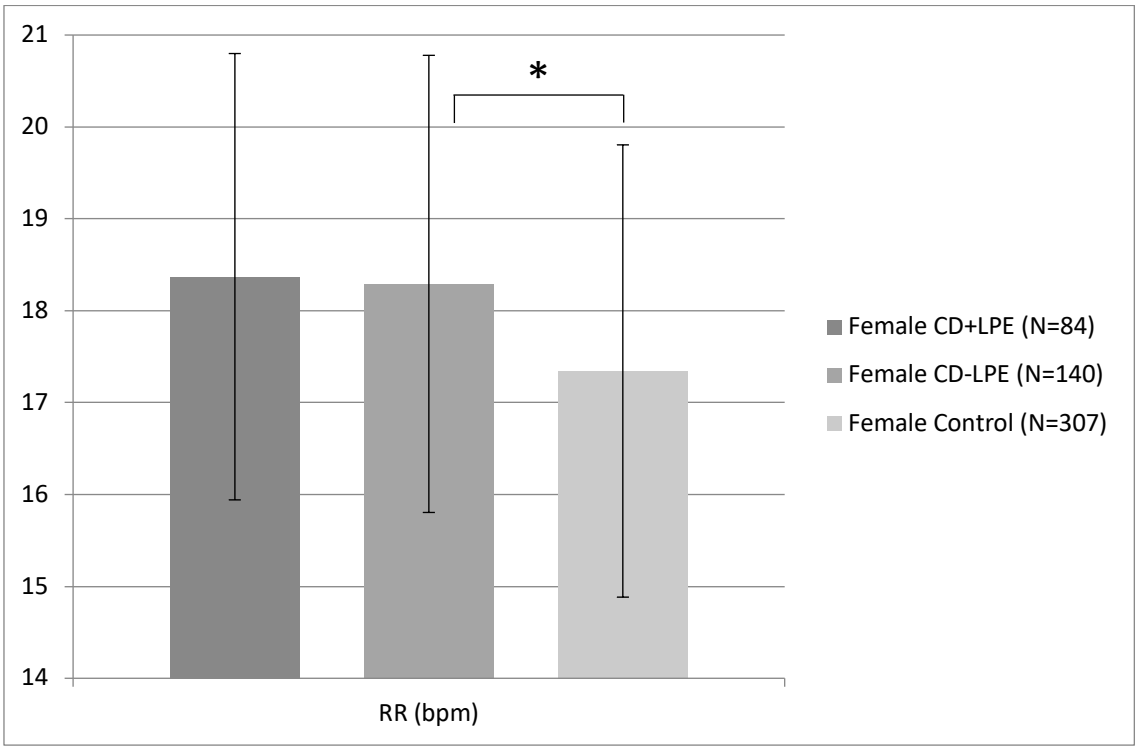

Fig. 2. Respiration Rate (RR) in CD Females fulfilling the LPE Specifier (CD + LPE), CD Females not fulfilling the LPE Specifier (CD-LPE), and Female Controls.

Note. Error bars show standard deviations, and * indicates significance at the .05 level.

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 ($F(2,536) = 3.847$, $p < 0.05$, $\eta p2 = 0.014$). 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.

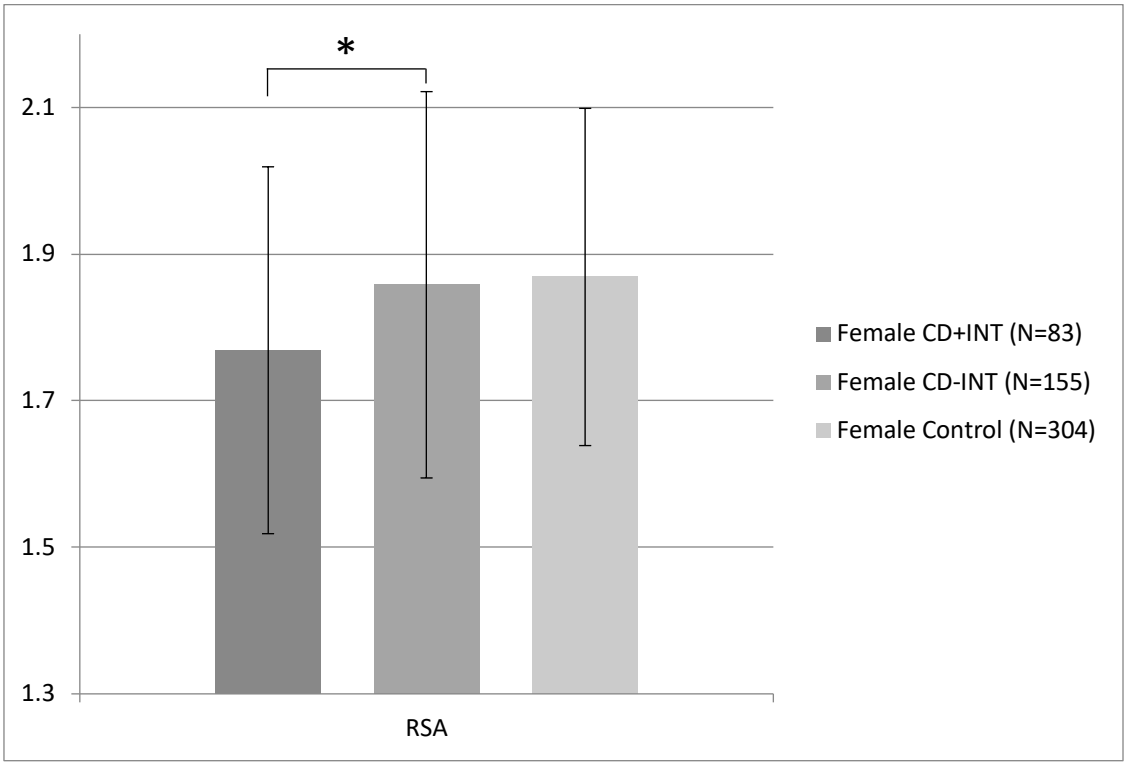

Fig. 3. Respirator Sinus Arrhythmia (RSA) in CD Females with a Comorbid Internalizing Disorder (CD + INT), CD Females without a Comorbid Internalizing Disorder (CD-INT), and Female Controls.

Note. Error bars show standard deviations, and * indicates significance at the .05 level.

We repeated the above analyses using lifetime diagnoses of comorbid internalizing disorders instead of current diagnoses. Statistical comparisons revealed the same results. 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 sub-group 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 Low 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. (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 (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 psychophysiolo- gical 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 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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Chapter 3 Resting autonomic nervous system activity is unrelated to antisocial behavior dimensions in adolescents: Cross-sectional findings from a european multi-centre study

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Abstract

Purpose: Autonomic nervous system (ANS) functioning has long been studied in relation to antisocial behaviour, but relevant measures (heart rate, heart rate variability, pre-ejection period, respiration rate) have rarely been considered together. This study investigated the relationship between these measures and antisocial behaviour.

Methods: Using a sample of 1,010 youths with (47.8%) and without conduct disorder (52.2%) aged between 9-18 years (659 females, 351 males, mean age=14.2 years, SD=2.4), principal component analysis (PCA) was applied to various measures of psychopathology and antisocial behavior. Structural equation modelling was performed in order to test whether the ANS measures predicted PCA-dimensions. Cluster analysis was used in order to classify patterns of ANS activity. Analyses were performed separately for males/females and controlled for body-mass-index, age, caffeine use, cigarette smoking, sports, socioeconomic status, medication, cardiac problems.

Results: The PCA yielded three components: antisocial behaviour/comorbid psychopathology, narcissistic traits, and callous-unemotional traits. ANS measures were only weakly correlated with these components. Cluster analysis yielded high and low arousal clusters in both sexes. When controlling for covariates, all associations disappeared.

Conclusion: Our findings suggest that resting ANS measures are only weakly related to antisocial behaviour and indicate that smoking should be considered as an important covariate in future psychophysiological studies.

Keywords: autonomic nervous system, antisocial behaviour, callous-unemotional traits, smoking, cluster analysis, sex

1. Introduction

Autonomic nervous system and antisocial behavior

Autonomic nervous system (ANS) functioning has long been studied in relation to antisocial behaviour (see Portnoy et al., 2014). Antisocial behaviour can be characterized by conduct problems, aggression, psychopathic tendencies, and also comprises delinquent behaviour. Together these represent major public health and societal concerns (Portnoy & Farrington, 2015). Conduct disorder is one clinical manifestation of severe antisocial behaviour and its diagnostic criteria include aggressive (e.g., fighting, bullying, vandalism) and rule-breaking behaviour in children and adolescents (e.g., lying, theft, truancy; (American Psychiatric Association, 2013)). Due to the heterogeneity of antisocial behaviour and conduct disorder, a number of attempts have been made to characterize various subtypes or phenotypes, e.g., proactive/reactive aggression, conduct disorder with elevated psychopathic/callous-unemotional traits or in combination with internalizing symptoms or previous traumatic experiences (Steiner, Daniels, Stadler, & Kelly, 2017). Callous-unemotional traits comprising a lack of empathy, reduced guilt or reduced affective responding have been identified as important subtyping characteristics of children and adolescents with antisocial behaviour, although callous-unemotional traits can also occur in typically-developing children and adolescents (Fanti, Demetriou, & Kimonis, 2013; Herpers, Rommelse, Bons, Buitelaar, & Scheepers, 2012; Raschle et al., 2017). On a physiological level, different ANS measures have been used to identify ANS deficits in antisocial populations, and linked to some of the neurocognitive difficulties that they show, such as impairments in emotion regulation or reward processing (Fanti, 2016; Matthys, Vanderschuren, & Schutter, 2013). However, most of the studies have used just a single measure of ANS functioning, such as heart rate (Portnoy & Farrington, 2015), whereas multiple measures are needed to provide a more comprehensive assessment of ANS profiles associated with antisocial behavior. Therefore, this study aims to investigate simultaneously four cardiorespiratory ANS markers, in order to shed more light on the links between the ANS and antisocial behavior. Furthermore, the measurement of multiple ANS parameters allows for a clustering of ANS measures which might reconcile inconsistencies caused by differences in assessment of psychopathological phenotypes (Fanti, 2016). In contrast to investigating categorically defined diagnoses, we will use a comprehensive assessment approach considering a broad spectrum of antisocial behavior and adopting a dimensional approach. For a categorical approach on this dataset, please see Oldenhof et al. (this volume).

Cardiorespiratory ANS measures and antisocial behaviour

Four cardiorespiratory ANS markers measuring sympathetic (SNS) and/or parasympathetic nervous system (PNS) activity have previously been related to antisocial behavior: (1) heart rate (SNS and PNS activity), (2) heart rate variability (PNS activity), (3) pre-ejection period (SNS activity), and (4) respiration rate (SNS and PNS activity). Several meta-analyses have confirmed low resting heart rate as a robust physiological correlate of antisocial behaviour including, e.g., aggression, psychopathy and conduct and oppositional defiant disorders (Ortiz & Raine, 2004; Portnoy & Farrington, 2015). Heart rate variability, in particular respiratory sinus arrhythmia, can be an indicator of cardiac PNS activity and is commonly quantified by spectral or time-domain analytic approaches (Grossman & Taylor, 2007). These approaches can also be used to derive many other parameters of heart rate variability (Allen, Chambers, & Towers, 2007). Reduced resting heart rate variability has been linked to externalizing and antisocial behaviour (Beauchaine, Gatzke-Kopp, & Mead, 2007; Graziano & Derefinko, 2013) and seems to be linked to lower emotion regulation abilities (Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012; Williams et al., 2015). Pre-ejection period has previously been associated with reward processing which is affected in conduct and oppositional defiant disorders (Matthys et al., 2013; Sidlauskaite et al., 2017). Thereby, a lengthened resting pre-ejection period - indicating less sympathetic activity - was found in relation to conduct problems and aggression in children (Beauchaine et al., 2013). Finally, research has increasingly recognized the importance of respiration in relation to cognitive and emotional processing (Zelano et al., 2016), which are impacted in antisocial youth (Raschle, Menks, Fehlbaum, Tshomba, & Stadler, 2015). A higher respiration rate has been associated with severity of internalizing problems in girls (Blom, Serlachius, Chesney, & Olsson, 2014) and respiration rate has been linked to emotions such as anger, disgust and anxiety (Kreibig, 2010). While an association between aggressive behaviour and respiration rate has been found in animals (Carnevali, Nalivaiko, & Sgoifo, 2014), respiration rate has not yet been investigated as a correlate of aggressive or antisocial behaviour in humans. The Polyvagal Theory has been used to explain the link between the ANS and antisocial behaviour (Beauchaine et al., 2007). Despite its highly regarded, explanatory role for research findings of psychopathology and emotion dysregulation (Beauchaine et al., 2007), its biological validity has been questioned, and the basic assumptions of the theory appear to have been falsified (Farmer, Dutschmann, Paton, Pickering, & McAllen, 2016; Gourine, Machhada, Trapp, & Spyer, 2016; Grossman, 2016; Grossman & Taylor, 2007).

Biological mechanisms

Neuroimaging studies have revealed biological mechanisms behind the autonomic arousal and antisocial behaviour relationship: Brain regions involved in autonomic control and emotion regulation partly overlap (Thayer et al., 2012; Thayer & Lane, 2000) and exhibit structural and functional alterations in youths with aggression (Raschle et al., 2015) and conduct problems (Rogers & De Brito, 2016). Aggression can be considered as deficient emotion regulation which reflects abnormalities in the underlying emotion regulation network of the brain (Davidson, Putnam, & Larson, 2000). The neuro-visceral integration model elaborates on the role of one of the affected regions, the prefrontal cortex, for emotional, cognitive and autonomic regulation (Thayer & Lane, 2009). Thus, the overlap of emotion and autonomic regulation warrants the use of ANS measures for the study of aggressive behaviour.

Gaps in the literature

Overall, it can be concluded that there is substantial evidence linking ANS markers with different aspects of antisocial behaviour. However, the four ANS markers have rarely been included together in the same study. Further, many previous studies had small sample sizes. In addition, numerous studies have highlighted the importance of including sex in the description of antisocial behavior dimensions and ANS activity (e.g., Koenig & Thayer, 2016; Lehto-Salo, Närhi, Ahonen, & Marttunen, 2009), but this has rarely been done. The majority of studies on ANS activity and antisocial behaviour have not systematically controlled for lifestyle factors that may differ between typically-developing and antisocial groups (Portnoy & Farrington, 2015), even though smoking, sports, caffeine use, body mass index (BMI), medication use, and socio-economic status have all been shown to influence ANS functioning and/or psychopathology (Alvares, Quintana, Hickie, & Guastella, 2016; Hu, Lamers, de Geus, & Penninx, 2017; Koenig et al., 2014; Martin et al., 2008; Piotrowska, Stride, Croft, & Rowe, 2015). In particular, the influence of smoking has only been examined in a few studies (Jennings, Piquero, & Farrington, 2013; Murray et al., 2016), despite evidence indicating that smoking constitutes a risk factor for the development of antisocial behaviour and impacts brain and ANS functioning (Hu et al., 2017; Pagani, Lévesque-Seck, Archambault, & Janosz, 2017).

Research aims

We aimed to disentangle the role of different ANS parameters in antisocial behaviour using data collected as part of a European multi-centre study (FemNAT-CD), with a specific focus on gender

differences. We hereby aim to overcome several limitations of the previous literature by: (I) including two mixed measures capturing both SNS and PNS activity (i.e. heart rate and respiration rate) and two measures capturing PNS (i.e. heart rate variability) and SNS (i.e. pre-ejection period) activity separately. This approach allows us (II) to identify distinct physiological phenotypes and relate them to antisocial behaviour. As respiration rate has only been investigated in animal research, we also studied the link between respiration rate and antisocial behavior (III). Moreover, we consider (IV) the influence of covariates such as smoking, sports, caffeine, BMI, medication, cardiac problems and socio-economic status. We set out to investigate our research aims in a sample including individuals with and without conduct disorder. In line with previous literature, we hypothesized that we would observe negative correlations between heart rate and respiratory sinus arrhythmia and antisocial behaviour, whereas we predicted that pre-ejection period and respiration rate would be positively correlated with antisocial behaviour. Further, we hypothesized that different ANS clusters would be associated with measures of antisocial behaviour.

2. Methods

2.1 Recruitment and participants

1010 adolescents (659 females, 351 males; 47.8% with conduct disorder and/or oppositional defiant disorder) aged between 9 and 18 years (mean = 14.2, SD = 2.4) were included in the study as part of an ongoing European multi-centre study investigating female conduct disorder (FemNAT-CD). The distribution of comorbidity patterns was as follows: conduct and oppositional defiant disorder (64.5%), conduct disorder only (23.7%), oppositional defiant disorder only (11.8%). A more detailed description of the sample characteristics (including ANS values) is provided in the article by Oldenhof et al. (this volume). The participants were recruited through schools, clinics, and youth welfare institutions in seven European countries (Germany, Greece, Hungary, Netherlands, Spain, Switzerland, and United Kingdom). All participants underwent standardized clinical interviews, filled out questionnaires and took part in an ANS measurement session. All individuals had to have an IQ >= 70 (see Fig. 1 for inclusion and exclusion criteria). Patients were diagnosed with conduct disorder based on a semi-structured clinical interview (please see section 2.2.2 below for details of the assessment). Written informed consent was obtained from the participants and their caretakers. The study was conducted in accordance with the Declaration of Helsinki and approved by all local ethics committees.

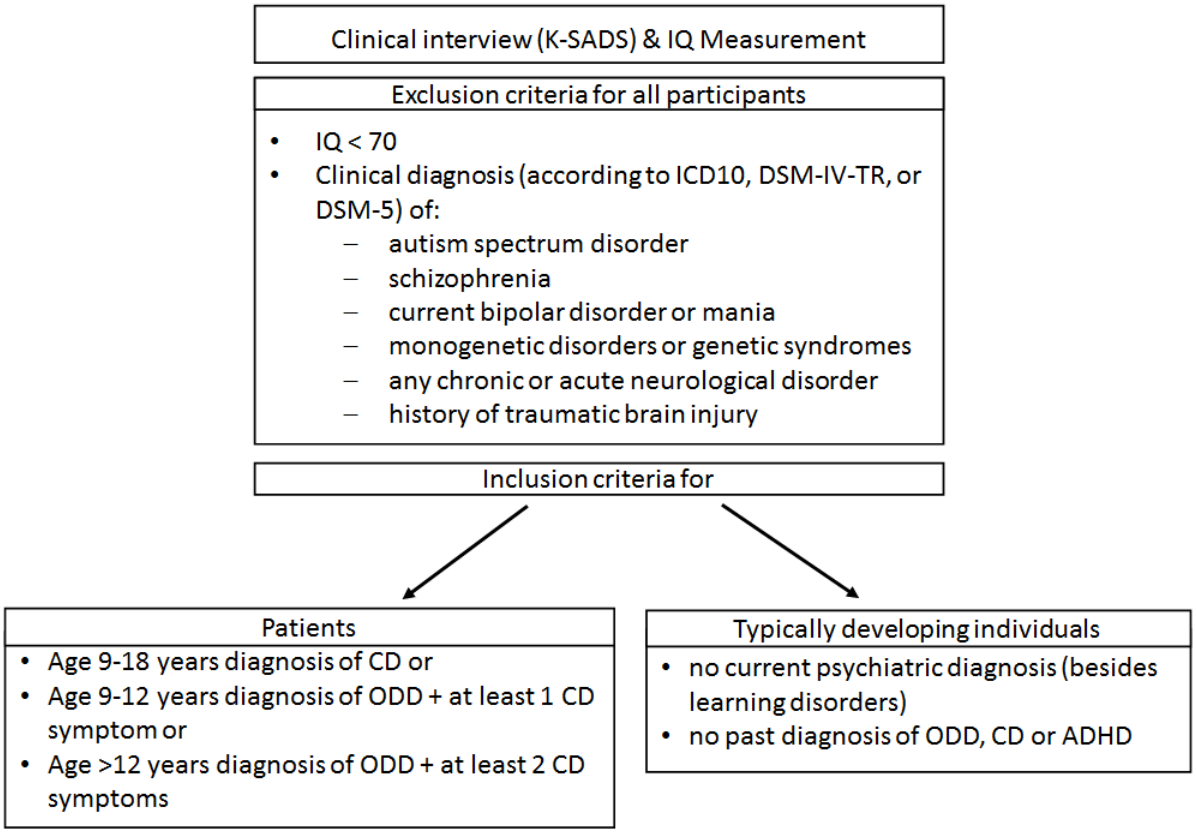

Figure 1. Inclusion and exclusion criteria in the study. CD=conduct disorder; ODD=oppositional defiant disorder; ADHD=attention deficit hyperactivity disorder.

2.2 Materials

2.2.1 ANS measures

ANS measures were assessed using electrocardiography (ECG) and impedance cardiography (ICG) registration by the VU-AMS device (Vrije Universiteit Ambulatory Monitoring System) (de Geus, Willemsen, Klaver, & van Doornen, 1995). H98SG, ECG Micropore electrodes (Covidien, Germany) were used and applied to the skin which was cleaned with alcohol beforehand. The R-peak time series were derived from the ECG data by an automated detection algorithm within the VU-DAMS software package version 3.9 and checked manually for missed or incorrect R-wave peaks and abnormalities in the registration. Abnormalities defined as premature ventricular contractions (PVCs), premature atrial contractions (PACs) or low quality ECG signal fragments 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-DAMS 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), and identified as 'irregular respiration' when the duration of consecutive breaths reached a threshold. Whenever > 50% of the respiration data was identified as 'irregular', respiration rate data was set as missing. Data checking and scoring were performed by trained researchers and students and additional consensus meetings took place in order to discuss complex data.

Heart rate in beats per minute was derived from the ECG signal derived R-peak time series and respiration rate in breaths per minute was derived from the thorax impedance signal. To investigate heart rate variability, as a measure of PNS activity, respiratory sinus arrhythmia was assessed. Respiratory sinus arrhythmia was calculated using the peak-valley method (Grossman, Beek, & Wientjes, 1990) by subtracting the shortest heart period during inspiration minus the longest heart period during expiration; this was computed on a breath-to-breath basis. When no difference in shortest and longest beats could be detected, respiratory sinus arrhythmia was set to be zero for that particular breath. Respiratory sinus arrhythmia values were set as missing when > 50% of the breaths could not be detected or were identified as 'irregular'.

Cardiac SNS activity was measured by the pre-ejection period (in ms). This is currently the most reliable non-invasive indicator of SNS activity (van Lien, Schutte, Meijer, & de Geus, 2013) and can be derived from combined ICG and ECG recording. Pre-ejection period 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.

Baseline measurement – After the ECG/ICG electrodes were applied to the participant's body, they were given 10 min to habituate to the procedure. This enabled the participant to get accustomed to the setting in order to minimize the effect of stress induced by the experimental setting. Thereafter, a 5-minute excerpt from an aquatic video (Coral Sea Dreaming, Small World Music Inc.) was presented to obtain baseline ANS measures, which was proven effective 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 or consumed alcohol or used drugs in the past 24 h. If they answered positively to any of these questions, the assessment was postponed.

2.2.2 Behavioural measures

Conduct disorder. Diagnostic information was obtained through 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-IV-TR/DSM-5 criteria (American Psychiatric Association, 2000, 2013). Interviews were conducted with the participant and their parent or caretaker separately. Additionally, information from medical files was used in some cases. Summary ratings are derived from the clinical judgment of the interviewer using all available sources.

IQ. In case of missing IQ measurements, the IQ was estimated using two subtests of the Wechsler Intelligence Scale for Children: vocabulary and block design, or for participants from the age 17 on the Wechsler Adult Intelligence Scale (Petermann & Wechsler, 2008): vocabulary and matrix reasoning. At UK sites, the Wechsler Abbreviated Scale of Intelligence (WASI) was used for all ages (Wechsler, 1999).

Psychopathic traits. We used the self-report version of the Youth Psychopathic traits Inventory (YPI) (Andershed, Kerr, Stattin, & Levander, 2002) to assess psychopathy. This questionnaire consists of 50 items scored on a 4-point Likert scale from 1 to 4, ranging from "Does not apply at all" to "Applies very well". The YPI comprises the following ten subscales: dishonest charm, grandiosity, lying, manipulation, remorselessness, unemotionality, callousness, thrill seeking, impulsiveness, irresponsibility. In our study, the subscales dishonest charm (α=.80) and manipulation (α=.81) showed good, the subscales lying (α=.77), remorselessness (α=.72), impulsiveness (α=.72) and irresponsibility (α=.75) acceptable, the subscales grandiosity (α=.68), unemotionality (α=.60) and thrill seeking (α=.66) questionable and the scale callousness (α=.57) poor internal consistency.

Comorbid psychopathology. We used the Massachusetts Youth Screening Instrument Version 2 (MAYSI-2) (Grisso & Barnum, 2006) to screen for a variety of comorbid psychopathological symptoms. The MAYSI-2 is a self-report tool developed to facilitate identification of youths with mental health issues within juvenile-justice facilities. The version we used in our study consists of 48 ‘yes’ or ‘no’ questions regarding the past 2-3 months. The instrument contains seven scales: ‘alcohol/drug use’ (ADU), ‘angry-irritable’ (AI), ‘depressed-anxious’ (DA), ‘somatic complaints’ (SC), ‘suicide ideation’ (SI), ‘thought disturbance’ (TD), and ‘traumatic experiences’ (TE). The scales ADU (α=0.89), AI (α=.85), DA (α=.79), SC (α=.75), SI (α=.89) showed good, the TD scale (α=.64) sufficient and the TE scale showed poor (α=.52) internal consistencies in our study, possibly due to the use of a shortened version of this scale containing only 2 items instead of 5.

Aggression. We used the Reactive-Proactive aggression Questionnaire (RPQ) (Raine et al., 2006) to distinguish between these types of aggression. The questionnaire consists of 23 items on a 3-point Likert scale from 0-2, ranging from "never" to "often". The proactive and reactive scales are sum scores of the respective items. The reactive (α=.88) and proactive (α=.86) scales showed good internal consistency in our study.

2.2.3 Covariates

Body mass index. Weight and height were measured on the day of the physiological assessment for the calculation of participants' body mass index (BMI).

Caffeine. We assessed caffeine use on the day of the physiological assessment by asking the participants: "How many caffeine-containing drinks (e.g., coffee, tea, coke, energy drinks) have you consumed in the past 24 hours?".

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).

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

Socioeconomic status. Socioeconomic status (SES) was estimated based on parental income, education and occupation. Assessments were based on the International Standard Classification of Occupations (International Labour Organization, 2012) and the International Classification of Education (UNESCO Institute for Statistics, 2015). Human rater and computer-based ratings were combined into a factor score using Principal Component Analysis (PCA). Reliability (internal consistency) of the composite SES score was acceptable (α =.74).

Medication. We assessed psychotropic medication by asking the participant, caretaker, therapist or parent. For the analysis, we integrated the information as a dichotomous variable (0 = no medication and 1 = medication).

Cardiac problems. We assessed cardiac problems as a dichotomous variable (yes/no) by asking the participant: "Have you had any heart problems in the past?" (e.g., cardiac arrhythmia/heart surgery).

2.3 Statistical analyses

2.3.1 ANS measures – data cleaning and preparation

Statistical analyses were performed using SPSS Version 24/AMOS Version 24 and R Version 3.4.2. Before analysis, data cleaning was applied to all ANS measures. We log-transformed respiratory sinus arrhythmia (lgRSA) due to a right-skewed distribution which became closer to a normal distribution

after transformation. Values higher or lower than 3 SD of the sample means were classified as outliers and excluded. For respiration rate we identified 5 outliers, for heart rate 1 missing value and 7 outliers, for pre-ejection period there were 50 missing values and 1 outlier, and for the respiratory sinus arrhythmia data 8 outliers. Additionally, for respiration rate we excluded all values which contained more than 50% of irregular respiration (identified by the VU-DAMS programme) in the 5 min baseline which was the case for 6 values. The respective respiratory sinus arrhythmia values were excluded as well. Subsequently, we checked whether the number of missing values and outliers differ in a systematic way between groups (gender and patient status). Summing up the number of missing values and outliers for all four ANS measures per individual, ANOVA was performed to identify group (gender and patient status) biases. No differences were observed between the groups. The values were excluded on a single value basis, id est, if for example the pre-ejection period value was excluded, the other ANS values of this participant were still included for analysis. Several analyses were conducted to identify potential site effects on ANS measures, e.g., due to differences in use of technical devices, climate or other local circumstances. Using a saturated model Analysis of Variance (ANOVA) on ANS measures (as dependent), patient status and gender (as fixed factors), site (as random factor) and age and testing time (as covariates), site did neither emerge as a significant main effect, nor within a significant interaction term, suggesting no bias caused by site effects.

2.3.2 Main statistical analyses

Principal Component Analysis (PCA) was performed separately for each sex, extracting orthogonal (uncorrelated) components with an Eigenvalue > 1 (Kaiser-Guttmann criterion). Standardized scores on PCA components for each individual were saved based on Bartlett-Regression. Bivariate correlations were conducted between the ANS measures, principal components and covariates. In a second step, partial correlations were used to control for the influence of covariates. Structural Equation Modelling (SEM) was performed using AMOS, with ANS measures, age and smoking as predictors and PCA components as outcome variables. Sex was included based on a two-group approach, allowing varying beta-coefficients for all paths and one common model fit for both sexes. Cluster Analysis was performed using R. At first, the R package “Mclust” (Fraley, Raftery, Murphy, & Scrucca, 2012) was used to identify the number of clusters using Bayesian Information Criterion (BIC) as a goodness-of-fit index. In a second step, k-means clustering (R package “stats”) was used to assess cluster membership for each individual based on the number of identified clusters in the first step. Cluster analysis was performed only on (standardized) ANS measures as continuous input variables, no questionnaires or other psychometric variables were included for cluster identification. Analyses of

Variance (ANOVA) were applied in order to test whether clusters differed on questionnaires and subscales included in the study, as well as on covariates and principal components obtained from PCA. The results obtained using cluster analysis were cross-validated with findings from Latent Class Analysis (LCA) using Mplus, based on the number of identified clusters in the first step. Phi coefficients are reported to show the agreement of the two methods.

3. Results

3.1 Dimensions of antisocial behaviour

Table 1 illustrates the results of the PCA performed separately for both sexes using measures from the antisocial behaviour spectrum, comprising conduct disorder, reactive/proactive aggression, psychopathic traits (YPI), and comorbid psychopathology (drug and alcohol use, internalizing symptoms, traumatic experiences, MAYSI). For males and females, the Kaiser-Gutmann-criterion suggested a three-component solution. For both sexes highly similar factors emerged, considering that factor loadings for each component showed a high correspondence across the sexes (r1=.89; r2=.99; r3=.77), indicating factorial invariance in particular for component 2. Component 1 appears as a "general factor of antisocial behaviour and comorbid psychopathology" with high loadings on all scales that capture the broader spectrum of antisocial behaviour, for both sexes, with the highest loading on aggression. Component 2 was labelled "narcissistic traits" based on the highest loadings on manipulation, dishonest charm, and grandiosity (YPI). Component 3 shows similar loadings for both sexes, but considering the lowest of all correlations (r3=.77) it also shows an indication of factorial non-invariance by sex. Component 3 was named "callous-unemotional" for girls as it loaded on scales of callousness (λ=.73) and unemotional (λ=.35). For boys, component 3 was named "callous-blunt" as it loaded positively on the scale callousness (λ=.56) and negatively on lying (λ=-.40). This latter dimension also showed high loadings on conduct disorder itself, alcohol and drug use and proactive aggression. All three components account for 61.4% of the variance for girls and 59.4% of the variance for boys.

Table 1. Principal Component Analysis (PCA) using measures of antisocial behavior and psychopathology

		FEMALES (N=659)			MALES (N=351)		
		Component 1	Component 2	Component 3	Component 1	Component 2	Component 3
		„General Factor“	**„Narcissistic Traits“**	**„Callous-Unemotional“**	**„General Factor“**	**„Narcissistic Traits“**	**„Callous-Blunt“**
Conduct Disorder	K-SADS	**.70**	-.15	.27	**.50**	-.25	**.44**
Dishonest Charm	YPI	**.63**	**.52**	-.26	**.61**	**.55**	-.15
Grandiosity	YPI	**.36**	**.54**	-.22	**.45**	**.50**	-.26
Lying	YPI	**.59**	**.34**	-.20	**.53**	**.37**	**-.40**
Manipulation	YPI	**.67**	**.50**	-.24	**.62**	**.57**	-.11
Remorselessness	YPI	**.67**	**.35**	.16	**.67**	**.38**	.04
Unemotional	YPI	**.50**	**.46**	**.35**	**.48**	**.49**	.19
Callousness	YPI	**.41**	.18	**.73**	**.39**	.24	**.56**
Thrill seeking	YPI	**.70**	.23	-.12	**.62**	**.34**	-.09
Impulsivity	YPI	**.73**	.05	-.09	**.67**	.20	-.16
Irresponsibility	YPI	**.75**	.01	.10	**.68**	.05	.26
Alcohol / Drug Use	MAYSI	**.68**	-.19	.00	**.60**	-.15	**.37**
Angry-Irritable	MAYSI	**.80**	**-.32**	-.01	**.76**	-.41	-.03
Depressed-Anxious	MAYSI	**.74**	**-.46**	-.02	**.66**	**-.50**	-.27
Somatic Complaints	MAYSI	**.50**	**-.48**	**-.32**	**.51**	**-.52**	-.27
Suicidal Ideation	MAYSI	**.68**	**-.34**	.07	**.53**	**-.40**	-.08
Thought Disturbance	MAYSI	**.58**	-.25	-.08	**.57**	**-.37**	-.23
Traumatic Experience	MAYSI	**.78**	**-.33**	.00	**.71**	**-.41**	-.17
Proactive Aggression	RPQ	**.75**	.01	.03	**.67**	-.12	**.30**
Reactive Aggression	RPQ	**.82**	-.13	-.01	**.75**	-.20	.16
Eigenvalue		8,33	2,24	1,09	7,14	2,86	1,29
% Variance		43,9%	11,8%	5,75%	37,6%	15,0%	6,8%

Note. Component extraction based on Kaiser-Gutmann-Criterion (Eigenvalue > 1); Bold loadings > .30 or <-.30;
K-SADS-PL = Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version; YPI = Youth Psychopathic traits Inventory; MAYSI-2 = Massachusetts Youth Screening Instrument 2; RPQ = Reactive-Proactive aggression Questionnaire; ”General factor” (GF) of antisocial behaviour and comorbid psychopathology

3.2 Correlations between antisocial behaviour, ANS measures and covariates

Table 2 shows a correlation matrix between the three principal components of antisocial behaviour and comorbid psychopathology identified in our analyses (see Table 1), the four ANS measures as well as covariates which are relevant for cardio-respiratory physiology and/or psychopathology. Correlations are shown for both sexes separately (females below the diagonal) and partial correlations controlled for covariates are superscripted. In females, significant correlations were observed between respiration rate and the general factor of antisocial behaviour ($r=.12$, $p<.01$) and callous-unemotional traits ($r=.08$, $p<.05$), and between heart rate and callous-unemotional traits ($r=.09$, $p<.05$), and pre-ejection period with the general factor of antisocial behaviour ($r=.14$, $p<.001$) and callous-unemotional traits ($r=-.09$, $p<.05$). In males, the pre-ejection period correlated positively with the general factor of antisocial behaviour ($r=.13$, $p<.05$) and callous-blunt traits ($r=.18$, $p<.01$), while respiratory sinus arrhythmia correlated negatively with narcissistic traits ($r=-.13$, $p<.05$). All significant correlations were rendered non-significant when we controlled for covariates.

Several significant correlations were observed between covariates, antisocial behaviour, and comorbid psychopathology. The most prominent association was found for smoking with the general factor of antisocial behaviour, with a higher correlation for girls ($r=.48$, $p<.001$) than for boys ($r=.38$, $p<.001$). In contrast, callous-blunt traits correlated significantly with smoking only in boys ($r=.41$, $p<.001$). Among the relation between covariates and ANS measures, age showed the strongest association with all of the ANS measures, especially in boys, whereas in females only respiration rate was not related to age. In boys, among the covariates, smoking was only related to pre-ejection period ($r=.23$, $p<.01$) whereas in girls smoking was related to respiratory sinus arrhythmia ($r=-.12$, $p<.01$), pre-ejection period ($r=.12$, $p<.01$), and respiration rate ($r=.20$, $p<.001$). Among ANS measures, significant correlations were observed in the expected direction, e.g., between respiratory sinus arrhythmia and heart rate (girls: $r=-.54$, $p<.001$; boys: $r=-.48$, $p<.001$), except for an unexpected negative correlation between respiratory sinus arrhythmia and pre-ejection period ($r=-.14$, $p<.01$) in girls. The analyses suggest that these significant, though weak correlations between ANS measures and psychopathological components are influenced by covariates, potentially by smoking and age which show the highest correlations with these measures.

Table 2. Correlation matrix of psychopathological principal components, autonomic nervous system (ANS) measures and covariates for females (below diagonal) and males (above diagonal)

		PCA of Antisocial and comorbid Psychopathology[1]			ANS measures				Covariates							
		GF	Narc.	CU	lgRSA	PEP	HR	RR	BMI	Caffeine	Smoking	Sports	Age	SES	Medication	CP
PCA of Antisocial and comorbid Psycho-pathology[1]	GF		0 (.11)	0 (-.28***)	-.03 (.08)	.13* (-.00)	.00 (.10)	-.02 (-.02)	.14*	.27***	.38***	.02	.25***	-.16**	.10	-.03
	Narc.	0 (.15**)		0 (.16*)	-.13* (-.12)	-.10 (-.03)	.03 (.12)	.03 (.00)	.05	-.02	-.03	.12	.09	.10	-.05	.01
	CB	0 (-.04)	0 (-.03)		-.10 (.03)	.18** (-.04)	-.07 (-.03)	.03 (.01)	.04	.11	.41***	-.07	.22***	-.20***	.12*	.02
ANS measures	lgRSA	-.04 (.04)	.07 (.03)	.00 (-.03)		-.10	-.48***	-.29***	-.14*	-.04	-.08	.02	-.21***	.10	-.09	.11*
	PEP	.14*** (.05)	0 (.01)	-.09* (-.05)	-.14**		-.22***	-.09	.20**	.09	.23**	-.03	.38***	-.06	-.01	-.01
	HR	-.02 (-.02)	-.03 (-.06)	.09* (.06)	-.54***	-.14**		.21***	-.07	.00	-.08	-.09	-.35***	-.03	.21***	-.02
	RR	.12** (.07)	-.03 (.00)	.08* (.04)	-.32***	.02 (.02)	.08*		-.05	.03	-.01	.04	-.27***	-.07	.16**	.02
Covariates	BMI	.21***	-.06	.04	-.00	.12**	-.07	.02		.07	.14*	.19**	.39***	-.14*	-.11	.04
	Caffeine	.18***	-.07	.09*	-.01	.05	-.03	.09*	.15***		.24***	.04	.19**	-.10	-.03	-02
	Smoking	.48***	-.08	.07	-.12**	.12**	.06	.20***	.19***	.31***		.13*	.38***	-.21**	.06	.11
	Sports	-.16***	.05	.09*	.07	-.08	-.05	-.05	-.09*	.01	-.12**		.12	-.04	-.03	.08
	Age	.25***	-.08*	-.14***	-.14***	.31***	-.21***	-.03	.37***	.23***	.31***	-.10*		-.05	-.14*	.01
	SES	-.27***	.09*	-.09**	.03	-.06	.02	-.07	-.16***	-.13**	-.24***	.12**	-.07		-.15**	-.04
	Medication	.21***	-.08*	.00	-.01	.01	.06	.03	.10*	.07	.17***	.00	-.02	-.09*		.09
	CP	.10**	-.07	-.03	-.11**	.03	.03	.02	.01	.10*	.16***	-.02	.06	-.01	.02	

Note. Pearson correlations. The results of partial correlations controlling for covariates are reported in parentheses and superscripted. GF=General factor of antisocial behaviour and comorbid psychopathology , Narc. = narcissistic traits, CU=callous-unemotional traits, CB=callous-blunt traits, RSA=respiratory sinus arrhythmia, PEP=pre-ejection period, HR=heart rate, RR=respiration rate, BMI=body-mass-index, CP=cardiac problems.
[1] Antisocial and comorbid Psychopathology relates to the dimensions identified by the Principal Component Analysis (PCA), which are reported in Table 1. *p<.05, **p<.01, ***p<.001

3.3 Predictors of antisocial behavior

Figure 2 demonstrates the result of a multi-group SEM for both sexes (CFI=.988 RMSEA=.021) using the principal components of antisocial behaviour and comorbid psychopathology from Table 1 as outcome variables. None of the ANS measures significantly predicted PCA dimensions (general factor of antisocial behaviour, narcissistic traits, callous-unemotional/blunt traits). The covariates "smoking" and "age" outperformed all ANS measures with respect to predicting PCA dimensions. Smoking showed the strongest association with the general factor of antisocial behaviour and comorbid psychopathology (girls: β=.44***, p<.001; boys: β=.33***, p<.001) and with callous-unemotional/blunt traits (girls: β=.12**, p<.01; boys: β=.41***, p<.001). Several paths are significant only for one sex, e.g., age predicts callous-unemotional traits only in girls (β=-.18***, p<.001), whereas in boys the association of age and callous-blunt traits is non-significant (β=.06). Age is only negatively correlated with respiration rate in boys (β=-.24***, p<.001) and smoking only positively correlated with respiration rate in females (β=.19***, p<.001). Residual errors (ε1, ε2, ε3) which are expected to be uncorrelated (since PCA produces uncorrelated components), are correlated in males (ε1 with ε3, r=.20***, p<.001). Figure 2 shows that ANS measures do not function as predictors of principal components underlying antisocial behaviour and psychopathology when controlling for age and smoking behaviour.

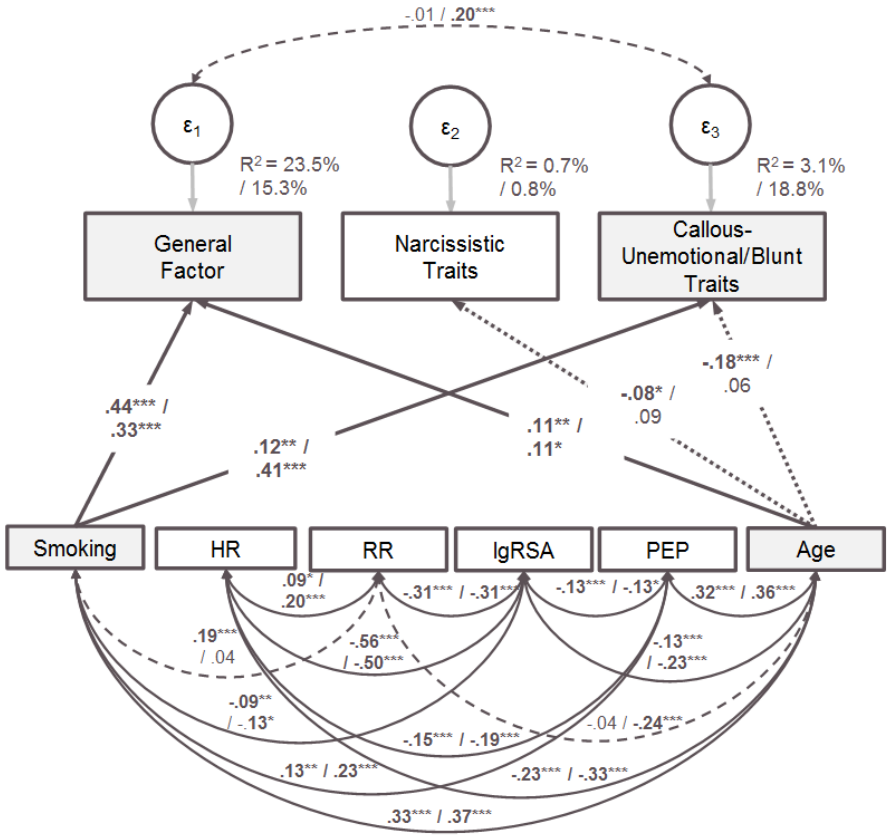

Figure 2. Structural Equation Model (SEM) using autonomic nervous system (ANS) measures as predictors of principal components analysis (PCA) dimensions of antisocial behavior and psychopathology controlling for age and smoking (CFI=.988 RMSEA=.021 df=34, N=1010) separately for females (parameters before slash) and males (parameters after slash) solid / dashed arrows represent significant paths for both sexes / significant paths only for one sex (*p<.05, **p<.01, ***p<.001). HR = heart rate, RR = respiration rate, RSA = respiratory sinus arrhythmia, PEP = pre-ejection period.

3.4 Physiological phenotypes

Figure 3 illustrates the results of a k-means Cluster Analysis performed on ANS measures based on a two-cluster solution for both sexes according to the Bayesian Information Criterion. For girls, the “high arousal” cluster (40.7% of the sample) is characterized by low respiratory sinus arrhythmia, high heart rate and high respiration rate. This cluster is also characterized by significantly higher levels of caffeine consumption and lower age. The second cluster (59.3% of the sample) displays an inverse pattern and therefore appears as a “low arousal” type. For boys, both clusters show similar ANS patterns compared to girls. One difference between the two sexes, however, relates to the pre-ejection period. For boys, the pre-ejection period is significantly higher in the “low arousal” cluster (67.9% of the sample). Contrarily, the clusters in girls do not differ with regard to pre-ejection period. The “high arousal” cluster (32.1% of the sample) is characterized by significantly lower age and lower smoking levels. In

females and males, there were no significant associations between cluster membership and psychopathological outcome variables (conduct disorder and principal components). Only in males, the "general factor of antisocial behaviour and comorbid psychopathology" showed evidence for a substantial difference between the two clusters. However, this association was no longer significant when controlling for multiple testing (Bonferroni correction), nor when controlling for covariates. ANOVAs were also performed on the subscales of each questionnaire, showing no significant associations between cluster membership and specific correlates of antisocial, aggressive, comorbid symptoms, callous-unemotional traits, and traumatic experiences (MAYSI, YPI, RPQ; data not shown). The cross-validation with findings from Latent Class Analysis using Mplus resulted in Phi coefficients of 0.75 for females and 0.83 for males.

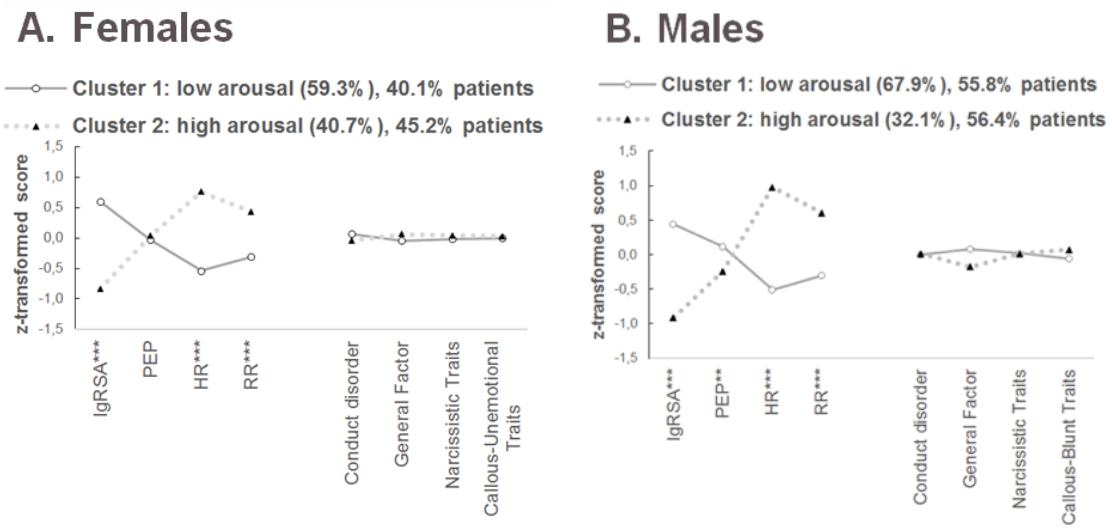

Figure 3. K-means cluster analysis performed using autonomic nervous system (ANS) measures as clustering variables and its relation to profiles across psychopathological principal components and conduct disorder for females (figure A) and males (figure B). Significant p-values of ANOVAs are shown (*** p<.001; **p<.01; * p<.05). RSA = respiratory sinus arrhythmia, HR = heart rate, PEP = pre-ejection period, RR = respiration rate.

4. Discussion

The aim of our study was to examine relationships between different dimensional measures of antisocial behaviour and several ANS measures determined under resting conditions. Furthermore, we investigated how different clusters of ANS activity relate to antisocial behaviour and comorbid psychopathology. We studied four ANS measures (heart and respiration rate, respiratory sinus arrhythmia and pre-ejection period) together capturing SNS and/or PNS activity. We carefully controlled for several covariates, including cigarette smoking. We studied those aspects with respect to sex using a large international sample including data acquired across seven European countries and containing not only healthy adolescents, but additionally those with clinically significant levels of antisocial behavior. This meant that we captured the full spectrum of antisocial behaviour – from very low to very high.

In our study, the weak correlations between baseline ANS measures and antisocial behaviour and psychopathology were rendered non-significant after controlling for age and smoking. Additionally, a cluster analysis suggested for both, girls and boys, a low and a high arousal cluster. Again, potentially significant (bivariate) associations between these ANS clusters and the general factor of antisocial behaviour and comorbid psychopathology were rendered non-significant when controlling for covariates.

No evidence for a relationship of low heart rate and antisocial behaviour

Some of our findings are in contrast to existing evidence regarding ANS functioning and antisocial behaviour. We did not find evidence for a relationship with low heart rate which had been shown in many previous studies (Latvala, Kuja-Halkola, Almqvist, Larsson, & Lichtenstein, 2015; Murray et al., 2016; Portnoy & Farrington, 2015). This is surprising, considering the statistical power based on a large sample size which tends to result in even small effects to become significant. However, in line with the present findings, a recent meta-analysis reported a trend showing the relationship between low resting heart rate and antisocial behaviour to become weaker with increasing publication year (Portnoy & Farrington, 2015). They explain this trend by referring to the “proteus phenomenon” describing an effect occurring in the early phase of a scientific investigation in which most likely significant findings are published in both directions. Later, findings refuting the original results become more interesting. Thus, the findings from Ortiz and Raine (2004) might have encouraged researchers to publish null findings refuting their results. One possible explanation of the weak relationship between antisocial behaviour and ANS parameters could be related to the severity of conduct problems in our study: Latvala et al. (2015) found a stronger relationship between violent crimes and low heart rate, as opposed to the comparison with non-violent crimes. Correspondingly, Portnoy and

Farrington (2015) showed the strongest effect size (d=−.35) for violence compared to the other categories of antisocial behaviour (aggression, behaviour problems, conduct disorder/oppositional defiant disorder, offending, psychopathy). The conduct disorder/oppositional defiant disorder category, which is also present in our sample, only exhibited an effect size of d=−.19 in their analysis for low heart rate. One might also argue that the use of an inclusive sample with patients and typically developing individuals could have masked possible relationships. To investigate this, a categorical approach was performed on the same sample by Oldenhof et al. (this volume). The authors compared the conduct disorder group with controls and found no relation between antisocial behaviour and heart rate - only a higher respiration rate in female cases compared to female controls was detected.

Weak relations between the remaining ANS measures and antisocial behaviour

All remaining ANS measures showed significant, but weak associations to antisocial behaviour and psychopathology. We found positive associations between pre-ejection period and antisocial psychopathology for both sexes. A lengthened resting pre-ejection period, indicating less sympathetic activity was previously found in relation to conduct problems in children (Beauchaine et al., 2013). Further, the positive relation between respiration rate and psychopathology in females had been shown before (Blom et al., 2014). A negative association between respiratory sinus arrhythmia and our narcissistic component in males is not in line with other findings indicating a positive link (Hansen, Johnsen, Thornton, Waage, & Thayer, 2007). After controlling for covariates, none of the associations remained significant. In general, our findings of weak ANS associations with antisocial psychopathology align with previous research. For example, heart rate variability exhibited quantitatively small to moderate associations to different types of psychopathology, with the exception of schizophrenia, exhibiting a large effect size (Alvares et al., 2016), which is hypothesised to be at the peak of severity of the general psychopathology factor (Caspi et al., 2014).

Considerations on the covariate smoking

Findings regarding the covariate smoking should be considered further. The positive association between smoking and antisocial and comorbid psychopathology is in line with prior research (Jennings et al., 2013; Pagani et al., 2017; Talati, Keyes, & Hasin, 2016). Interestingly, the association of smoking and antisocial psychopathology strengthened in more recent study cohorts, whereas at the same time the prevalence of smoking decreased (Talati et al., 2016). It is argued that as social desirability of smoking decreases, the prevalence of biologically vulnerable persons among the population of smokers increases. It is further discussed by Talati et al. (2016) that the risk for deviant behaviour and for psychiatric conditions, including substance use, share common genetic variance. Accordingly, two genome-wide association studies have found genes in adults with alcohol dependence to be possibly

related to conduct disorder in the past (Dick et al., 2011; Jian, Wang, Wu, Hillhouse, & Mullersman, 2011) and a strong overlap between substance abuse and antisocial behaviour has previously been shown (Krueger, Markon, Patrick, Benning, & Kramer, 2007).

ANS clusters

A further aim was to examine if reversing the common approach of relating psychopathology to physiology would benefit the investigation of the ANS and antisocial behaviour. For boys and girls a high and a low arousal cluster arose from our analysis. The results showed two opposite and physiologically plausible clusters, i.e., the ANS measures showed the expected relationships with each other (e.g., for heart rate and respiratory sinus arrhythmia an inversed activity pattern in both clusters). Previous research would suggest differential associations to psychopathology for these patterns, e.g., internalizing symptoms being related to higher ANS activity, and callous-unemotional traits being linked to lower ANS activity (Fanti, 2016). Our data does not provide evidence for such associations. The male clusters show a significant bivariate difference on the general factor of antisocial behaviour and comorbid psychopathology. However, the difference did not remain significant, neither after correcting for multiple testing, nor when controlling for covariates. Further, from a methodological point of view, an artificial division of study populations based on continuous variables, in our study the clustering based on ANS measures, may impact on results: It has been argued that a dichotomization of continuous measures leads to a loss of information and potentially leads to spuriously increased or decreased effects (MacCallum, Zhang, Preacher, & Rucker, 2002). In conclusion, also the reversed approach of creating groups of individuals based on resting ANS activity does not account for substantial variance in antisocial behaviour and comorbid psychopathology. The finding that patients were equally distributed over both clusters highlights the limited value for classifying individuals based on baseline ANS measures.

Limitations

Limitations of this study are considered, notably that we only assessed basal ANS measures. Growing evidence highlights the importance of ANS reactivity for adaptive functioning (Graziano & Derefinko, 2013). It is possible that we would have found associations between ANS activity and antisocial behaviour if we had included ANS reactivity measures in our analyses (e.g., heart rate increases to stress or in response to aversive stimuli). Despite acceptable reliability of SES (Cronbach's Alpha =.74), further limitations concern the inter-rater reliability of SES.

Suggestion for future research

Our study leads to some suggestions for future research. Considering the close relationship between smoking and respiration rate, at least in females, it would be worthwhile to include other respiratory variables in future studies (e.g., tidal volume, variability, pCO2), as they have been related to internalizing problems which are of direct relevance to the study of antisocial behaviour. Considering the strong relationship between antisocial behaviour and smoking and its relevance to ANS functioning, we recommend to assess smoking routinely in studies of ANS and antisocial behaviour. Ideally, it should be assessed as a continuous variable, given its non-linear relationship to pre-ejection period (Hu et al., 2017), allowing a more informative analysis.

Conclusion

In conclusion, we found that baseline ANS measures showed only weak associations with antisocial behaviour and comorbid psychopathology, all of which become insignificant when controlling for covariates. Smoking was strongly related to the general factor of antisocial behaviour and comorbid psychopathology, as well as callous-blunt traits, which implies the importance to consider this variable when studying antisocial behaviour. The finding of opposing ANS clusters for both sexes did not help to elucidate the relationship between resting ANS activity and antisocial behaviour. The positive association between respiration rate and antisocial behaviour in females warrants the inclusion of this measure in future studies on ANS activity and antisocial behaviour.

Practical implications

Given the small associations between the ANS and antisocial behaviour and comorbid psychopathology, our results do not support a potential of the ANS markers, as measured in a resting state, for profiling or predicting antisocial behaviour. However, future research should examine, if ANS markers examined under conditions of reactivity, for example, using an induction of emotions with film clips, provide such potential applications for the criminal justice practice. The strong relationship between smoking and antisocial behaviour suggests the relevance to target it in intervention and prevention programs, given its detrimental health effects to adolescents and their environment. Even passive smoking in households has been shown to increase the risk of antisocial behaviour (Pagani et al., 2017). Furthermore, females should be considered more carefully in intervention and prevention programs, as prenatal smoking constitutes a risk factor for the development of antisocial behaviour (Paradis, Shenassa, Papandonatos, Rogers, & Buka, 2017). Thus, the continuity of antisocial behaviour could potentially be decreased by placing a stronger focus on smoking prevention.

Competing interest

CMF has served as consultant for Desitin and Roche on Autism Spectrum Disorder. She receives royalties for books on ASD, ADHD, and depressive disorder. SDB 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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Chapter 4 Altered neuronal responses during an affective Stroop task in adolescents with conduct disorder

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Abstract

Conduct disorder (CD) is a psychiatric disorder of childhood and adolescence which has been linked to deficient emotion processing and regulation. The behavioral and neuronal correlates targeting the interaction of emotion processing and response inhibition are still investigated. Whole-brain event-related fMRI was applied during an affective Stroop task in 39 adolescents with CD and 39 typically developing adolescents (TD). Participants were presented with an emotional stimulus (negative/neutral) followed by a Stroop task with varying cognitive load (congruent/incongruent/blank trials). fMRI analysis included standard preprocessing, region of interest analyses (amygdala, insula, ventromedial prefrontal cortex) and whole-brain analyses based on a 2(*group*)x2(*emotion*)x3(*task*) full-factorial ANOVA. Adolescents with CD made significantly more errors, while reaction times did not significantly differ compared to TD. Additionally, we observed a lack of downregulation of left amygdala activity in response to incongruent trials and increased anterior insula activity for CD relative to TD during affective Stroop task processing (cluster-level FWE-corrected (p<.05)). Even though no three-way interaction (*group* x *emotion* x *task*) interaction was detected, the findings presented still provide evidence for altered neuronal underpinnings of the interaction of emotion processing and response inhibition in CD. Moreover, our results may corroborate previous evidence of emotion dysregulation as a core dysfunction in CD. Future studies shall focus on investigating the interaction of emotion processing and response inhibition in CD subgroups (e.g., variations in callous-unemotional traits, impulsivity, or anxiety).

Keywords: Conduct disorder, emotion processing, response inhibition, amygdala, insula

Introduction

Conduct disorder (CD) is a psychiatric disorder of childhood and adolescence marked by aggressive behavior outside of the age-appropriate norm (American Psychiatric Association, 2013). CD youths are more likely to engage in antisocial behavior (e.g., rule breaking, stealing, and lying (Lahey & Waldman, 2012)), and are at risk for academic failure, delinquency, and mental disorders in adulthood (Biederman et al., 2008; Erskine et al., 2016; Fergusson, John Horwood, & Ridder, 2005; Swanson, 1994). Antisocial youths are phenotypically characterized by a heterogeneous symptomatology, reflected in different aetiological paths and variations in response to treatment (Steiner, Daniels, Stadler, & Kelly, 2017). Four main forms of neurocognitive dysfunctions relating to the development, heterogeneity, and core impairments of CD have been proposed: reduced affective empathy, threat sensitivity, decision-making, and response inhibition (Blair, Veroude, & Buitelaar, 2016). In particular, the mechanisms underlying deficient emotion processing and response inhibition have been hypothesized to increase the risk for antisocial behavior (Campbell, Shaw, & Gilliom, 2000; Davidson, Putnam, & Larson, 2000; Wang, Chassin, Lee, Haller, & King, 2017; Young et al., 2009). More specifically, top-down attention involved in the interaction of emotion processing and response inhibition might be related to dysfunctional emotion regulation observed in adolescents with CD (Hwang et al., 2016).

While altered response inhibition has been observed in adolescents with disruptive behavior disorders (DBD, including CD (Hwang et al., 2016; Prateeksha, Roopesh, & Vijayasagar, 2014), results are inconsistent in regards to the direction of findings. Some studies measuring response inhibition report no differences in performance of CD or DBD youths (Banich et al., 2007; Rubia, Halari, et al., 2010; Rubia et al., 2008). Others indicate higher error rates and/or longer reaction times (RTs) (Euler, Sterzer, & Stadler, 2014; Hwang et al., 2016; Prateeksha et al., 2014; Rubia, Halari, et al., 2009). Importantly, when response inhibition is preceded by emotional stimuli, decreases in performance are more commonly reported (Euler et al., 2014; Hwang et al., 2016; Prateeksha et al., 2014).

Studies using functional magnetic resonance imaging (fMRI) have shed light on the neuronal phenotype characteristic for CD youths. Most commonly, alterations in neural recruitment in frontal and limbic lobes (including insula, amygdala, and anterior cingulate) are reported (Blair, 2010; Hwang et al., 2016; Raschle, Menks, Fehlbaum, Tshomba, & Stadler, 2015; Rubia, 2011; Stadler et al., 2007; Sterzer & Stadler, 2009), which are likely to depend on the levels of callous-unemotional traits (Baker, Clanton, Rogers, & De Brito, 2015; Blair, 2010). Previous studies investigating response inhibition (e.g., stop, Simon, switch, or Stroop tasks) in CD have revealed decreased and increased neuronal activity in

medial prefrontal cortex, insula, cingulate gyrus, temporoparietal junction, subcortical regions, and occipital lobe (Banich et al., 2007; Rubia, Halari, et al., 2010; Rubia, Halari, et al., 2009; Rubia et al., 2008). To our knowledge, only one study has yet directly tested the interaction of emotion processing and response inhibition in DBD youths. In this study, Hwang et al. (2016) detected reduced ventromedial prefrontal cortex (vmPFC) and amygdala activity in response to negative affective stimuli and reduced insula activity with increasing cognitive load in DBD compared to typically developing (TD) youths.

The present study aims at adding to this first evidence in DBD by investigating the neuronal and behavioral correlates of the interaction of emotion processing and response inhibition in CD youths through fMRI during affective Stroop task performance. Using both region of interest and whole-brain approaches, we hypothesized (I) to observe *emotion* x *task* interactions for the Stroop effect (i.e., delayed RTs for trials with increased cognitive load and prior negative stimulation) in CD compared to TD youths, in line with previous work (Euler et al., 2014); (II) to detect reduced neuronal activity within brain regions involved in emotion processing and response inhibition (amygdala, insula, and vmPFC) during the affective Stroop task in CD relative to TD youths in line with previous findings (Hwang et al., 2016).

Methods

Participants

Seventy-eight youths (39CD/39TD) were included in the present analyses (age range: 10.1-19.1 years, mean age: 15.7 years, 10 females in each group, 10 males in each group were assessed in Berlin). CD was diagnosed according to DSM-5 criteria. Seventeen CD youths (43.6%) additionally met DSM-5 criteria for present attention-deficit hyperactivity disorder (ADHD), while 20 CD youths (51.3%) additionally met diagnostic criteria for oppositional defiant disorder (ODD). TD were included if no current psychiatric diagnosis was reported by either the participant and/or the parents/legal guardians. CD and TD groups were matched for age ($t(76)=.87$, $p=.390$) and non-verbal IQ ($t(76)=-.72$, $p=.472$) (Table 1/SI1). Moreover, both CD and TD groups from Basel and Berlin did not differ in age (CD: $t(37)=1.04$, $p=.303$; TD: $t(37)=-.92$, $p=.365$) or non-verbal IQ (CD: $t(37)=1.12$, $p=.269$; TD: $t(37)=1.47$, $p=.151$). Participants were recruited through referrals from child and adolescent psychiatric institutions, public schools, and the general public through the use of fliers.

Ethical considerations

All adolescents and parents/legal guardians gave written informed consent as approved by the local ethics committee 'Ethikkommission der Nordwest- und Zentralschweiz' and received vouchers for their participation.

Clinical testing and questionnaires

CD youths and their legal guardians completed the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime version (K-SADS-PL; Kaufman et al., 1997) in order to assess CD criteria and comorbid disorders according to the DSM-5 (Table 1). CD and TD participants completed the Youth Psychopathic traits Inventory (YPI, Andershed, Hodgins, and Tengstrom (2007)) and the matrix reasoning subtest of the WISC-IV (ages ≤16y; Petermann, U. (Eds.) (2011)) and the WAIS-III (ages ≥17y; Petermann (1997)) measuring non-verbal IQ. For 10 participants (9 CD, 1 TD), only a composite IQ score was obtained. CD and TD legal guardians moreover completed a socioeconomic status (SES) questionnaire (SI2). Participants were asked to report any medication administered prior to the MRI session (SI3). Exclusion of participants with medication revealed similar results in significant region of interest (ROI) and whole-brain analyses.

fMRI task: The affective Stroop task

We applied an affective number Stroop task as previously described in Raschle et al. (2017) (Figure 1). Each trial started with an emotional stimulus, i.e., a negative (Neg) or neutral (Neu) stimulus (150ms), followed by a task trial (congruent/incongruent/neutral Stroop trial or a blank screen) and finally a relaxation period, i.e., blank screen (350ms). All pictures were selected from a child-appropriate image system (Developmental Affective Photo System (DAPS); Cordon, Melinder, Goodman, and Edelstein (2013)). During task trials, participants were presented with an array of 1 to 4 digits or a blank screen and were asked to press a button corresponding to the number of items displayed. The number of items was either congruent (C; e.g., number 3 in an array of 3) or incongruent (IC; e.g., number 1 in an array of 2) with the digits presented. Star shaped stimuli (S; as a neutral baseline counting condition) and blank trials (B; no response expected from participants) were used as control conditions (for further details see Raschle et al. (2017)). Trial order and interstimulus intervals (which were 350–1850ms) were randomized using Optseq (http://surfer.nmr.mgh.harvard.edu/optseq) and kept constant across participants. A total of 300 task and 100 blank trials were administered (100 for C/IC/S

trials, 50 with preceding negative images, 50 with neutral images, in 2 runs), with a total scan time of about 16 minutes (7.59 min each run).

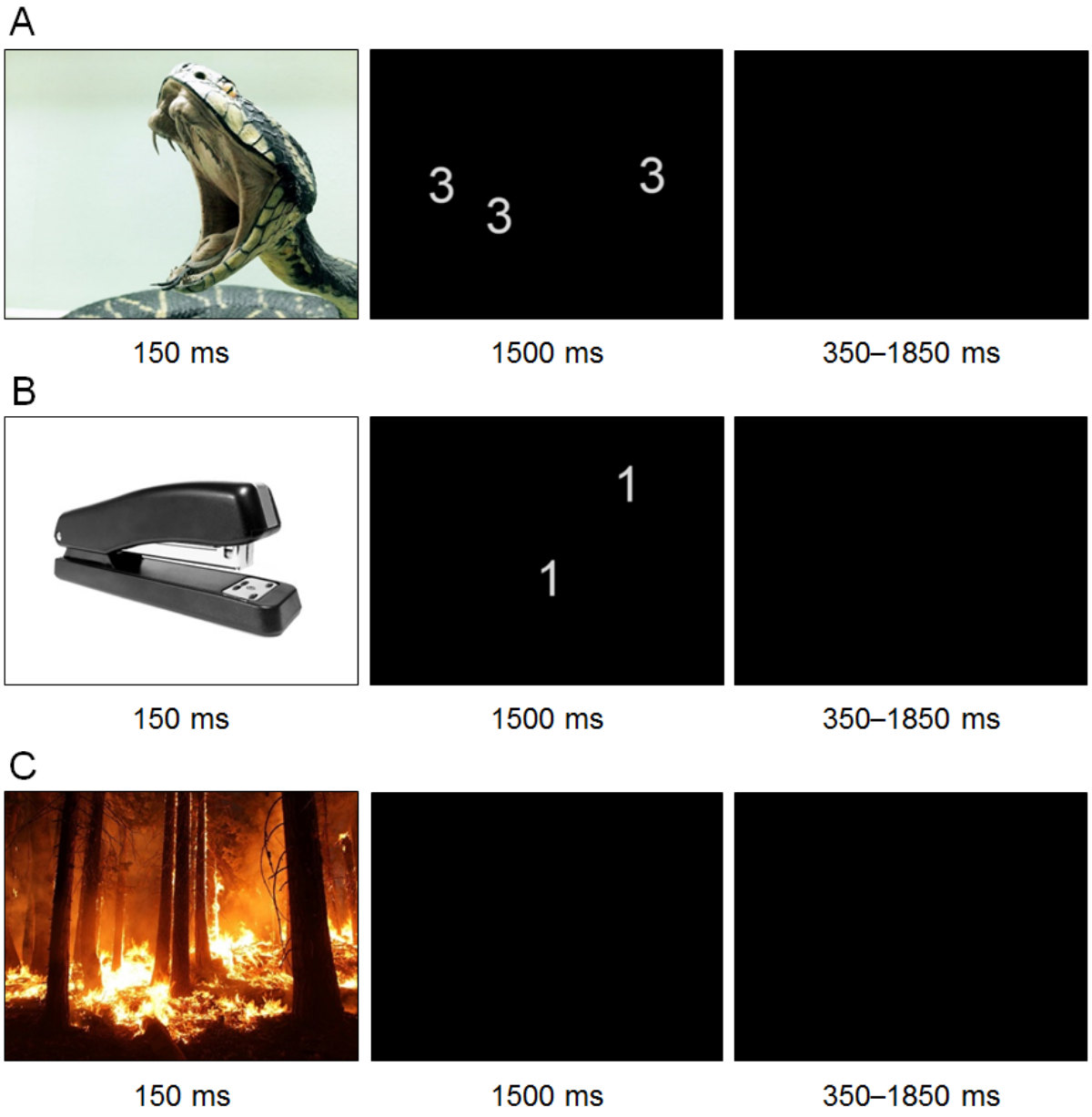

Figure 1 (to be published in color)**.** fMRI task design including three example affective Stroop trials. A: negative-congruent trial; B: neutral-incongruent trial; C: negative-blank trial.

Behavioral measures: In-scanner performance

All participants scored <60% correct responses per task condition and run. RTs and task accuracy (raw scores) were analyzed using 2x2x2 full-factorial ANOVAs with the between-subject factor *group* (CD, TD) and within-subject factors *emotion* (negative, neutral) and *task* (congruent, incongruent) for RTs and accuracy separately using SPSS, version 24. Data was unavailable for a minority of responses because of technical difficulties with the response box (for a detailed description see SI4).

fMRI data acquisition and analysis

Acquisition parameter. In Basel, whole-brain blood oxygen level-dependent (BOLD) fMRI data and structural T1-weighted magnetization prepared rapid gradient echo imaging images were acquired on a Siemens 3T Prisma MRI system using a 20-channel phased-array radio frequency head coil. In Berlin, a Siemens 3T TimTRIO MRI system equipped with a 12-channel head coil was used. At both sites a T2*-weighted EPI (echo-planar imaging) sequence with TR=2000ms, TE=30.0ms, FOV=192mm, image matrix=64x64mm, voxel size=3x3x3mm, and number of slices=37 was used. We further acquired high-resolution T1-weighted structural images for coregistration during fMRI preprocessing using the following specifications: TR=1900.0ms, TE=3.42ms, FOV=256mm, image matrix=256x256, voxel size=1mm.

fMRI Analysis. fMRI data were analyzed using the Statistical Parametric Mapping software, version 12 (SPM12, www.fil.ion.ucl.ac.uk/spm/). Preprocessing of the data included realignment, co-registration to the structural image, segmentation, normalization to the Montreal Neurologic Institute (MNI) standard brain, and spatial smoothing using an 8mm Full Width at Half Maximum Gaussian kernel.

Single-subject fMRI data was analyzed using the general linear model. The model comprised eight task regressors (each combining a negative or neutral stimulus with congruent, incongruent, or neutral (stars/blank) Stroop trials, namely negative-congruent (NegC), negative-stars (NegS), negative-incongruent (NegIC), negative-blank (NegB), neutral-congruent (NeuC), neutral-stars (NeuS), neutral-incongruent (NeuIC), neutral-blank (NeuB)), one regressor for incorrect/missed responses, and six motion regressors. The task regressors were modeled as stick functions convolved with the hemodynamic response function as implemented in SPM12.

At the second level, hypothesis-based ROI and whole-brain analyses were performed. A-priori defined ROIs included bilateral amygdala, insula, and vmPFC according to (Hwang et al., 2016; Raschle et al., 2015; Rubia, 2011; Rubia, Cubillo, et al., 2010; Rubia, Halari, et al., 2009; Rubia et al., 2008) and derived from the automated anatomical labeling atlas (aal; Tzourio-Mazoyer et al. (2002)). Mean parameter estimates were extracted from each ROI using the marsbar toolbox (Brett, Anton, Valabregue, & Poline, 2002). A repeated measures ANOVA with the factors *group* (CD, TD), *emotion* (negative, neutral), and *task* (blank, congruent, incongruent) and follow-up pairwise comparisons applying a Bonferroni multiple comparisons correction in order to account for the number of ROIs were then computed within SPSS, version 24.

For whole-brain analyses, beta images resulting from first-level model estimation for each regressor and run were submitted to a group-level random-effects analysis using a 2x2x3 full-factorial ANOVA with the between-subject factor *group* (CD, TD) and within-subject factors *emotion* (negative, neutral) and *task* (blank, congruent, incongruent).

Quality control was performed throughout the analyses in order to control for effects of motion. Besides including six additional motion regressors during single-subject analysis, each analysis mask was visually inspected for head motion. For all analyses, *site* (Basel, Berlin) was added as an additional factor of no interest. Brain activation was assessed for the main effects of *group*, *emotion*, and *task*, and all possible interactions thereof are reported at a cluster-extent family-wise error (FWE) rate of $p<.05$ (cluster building threshold of $p<.001$). Significant clusters of main effects and interactions were followed up with masked post-hoc *t*-tests.

Results

Questionnaires

Psychometric assessments are reported in Table 1. CD scored significantly higher than TD in the callous-unemotional and impulsive-irresponsible dimensions and the total score of the YPI (all $p<.01$; YPI, Andershed et al. (2007)). Nevertheless, psychopathic traits in our CD group were overall low (YPI total score: $M=11.16$, $SD=2.38$, CU dimension: $M=11.23$, $SD=3.08$; see also Stadlin, Pérez, Schmeck, Gallo, and Schmid (2016)).

Table 1. Behavioral group characteristics.

		CD	TD	*p*	
		Mean ± SD	Mean ± SD	Sig. 2-tailed	
		N=39	*N*=39		
Age (in years)		15.94 ± 1.88	15.54 ± 2.15	.390	
Sex (male/female)		29/10	29/10		
No. per site (Basel/Berlin)		11/28	11/28		
Handedness (right/left/both)		36/2/2	37/2/1		
IQ	Matrix reasoning	99.47 ± 12.02	101.54 ± 11.31	.472	
Comorbidities (DSM-5)	Attention-deficit hyperactivity disorder	17	0		
	Oppositional defiant disorder	20	0		
	Major depression	2	0		
	Anxiety disorder	6	0		
YPI		*N*=39	*N*=38		
	Grandiose-manipulative dimension	8.68 ± 2.74	7.89 ± 1.90	.117	
	Callous-unemotional dimension	11.23 ± 3.08	9.55 ± 1.94	.006	**
	Impulsive-irresponsible dimension	13.57 ± 2.80	10.68 ± 1.72	<.001	***
	Total score	11.16 ± 2.38	9.37 ± 1.21	<.001	***

*p<.05; **p<.01; ***p<.001, two-tailed t-test; all other t-tests non-significant at threshold p=.05

For IQ, standard scores are reported; for YPI, mean scores are reported.

CD=conduct disorder patients; TD=typically developing adolescents; SD=standard deviation.

Behavioral results: In-scanner performance

Analysis of RTs revealed a significant main effect of *emotion* (Neu>Neg, $F(1,76)=5.74$, $p<.05$), and a main effect of *task* (IC>C, $F(1,76)=615.48$, $p<.001$). There was no main effect of *group* and no interaction effects for RTs. For accuracy, we found a significant main effect of *emotion* (Neu>Neg, $F(1,76)=8.29$, $p<.01$), a main effect of *task* (C>IC, $F(1,76)=118.42$, $p<.001$), and a main effect of *group* (CD<TD, $F(1,76)=6.77$, $p<.05$). There were no significant interaction effects for accuracy (SI5).

Functional MRI results

ROI results. ROI analyses in relevant regions of interest (bilateral amygdala, insula, and vmPFC) revealed significant main effects of *emotion* and *task*, as well as *group* x *task* and *emotion* x *task* interactions.

Main effect of emotion. A significant main effect of *emotion* ($F(1,74)=7.12$, $p<.01$) was detected in left amygdala, driven by increased neuronal activity for negative compared to neutral trials (Neg>Neu, $p<.01$) (Figure 2).

Main effect of task. A significant main effect of *task* was detected in right ($F(2,73)=5.40$, $p<.01$) and left vmPFC ($F(2,73)=9.36$, $p<.001$), resulting from relatively decreased activation for incongruent compared to both blank and congruent trials (IC<B $p<.001$; IC<C, $p<.005$) for the left hemisphere and incongruent compared to blank trials for the right hemisphere (IC<B, $p<.005$).

Group x *task interaction.* A *group* x *task* interaction was observed in left amygdala ($F(2,73)=4.83$, $p<.05$), reflecting significantly decreased activity for incongruent compared to blank trials in TD (IC<B, $p<.05$), but not CD (all $p>.227$). This effect was independent of emotion (no significant *group* x *emotion* x *task* interaction; $F(2,73)=.73$, $p=.485$).

Emotion x *task interaction.* A significant *emotion* x *task* interaction effect was found in right amygdala ($F(2,73)=4.77$, $p<.05$). Across all subjects we observed relatively increased right amygdala activity for blank trials with a prior negative compared to neutral emotion (NegB>NeuB, $p<.05$), but relatively decreased activity in the right amygdala during congruent trials with a prior negative versus neutral emotion (NegC<NeuC, $p<.05$). In addition we observed decreased activity in the right amygdala for congruent relative to blank trials following negative stimuli (NegC<NegB, $p<.01$). Within right insula, a significant *emotion* x *task* effect was observed ($F(2,73)=5.40$, $p<.01$). This effect reflected increased activity during congruent trials following negative compared to neutral stimuli (NegC>NeuC, $p<.005$)

and increased activity for incongruent compared to congruent trials after negative stimuli (NegIC>NegC, *p*=.001). Decreased right insula activity was moreover detected for congruent compared to blank trials following negative stimuli (NegC<NegB, *p*<.001).

In order to examine the relationship between psychopathic traits (YPI total score) and left amygdala activity during IC–C (*group* x *task* interaction), follow-up bivariate correlations were computed for CD and TD separately. Results revealed no significant relationships between left amygdala activation and psychopathic traits for CD or TD.

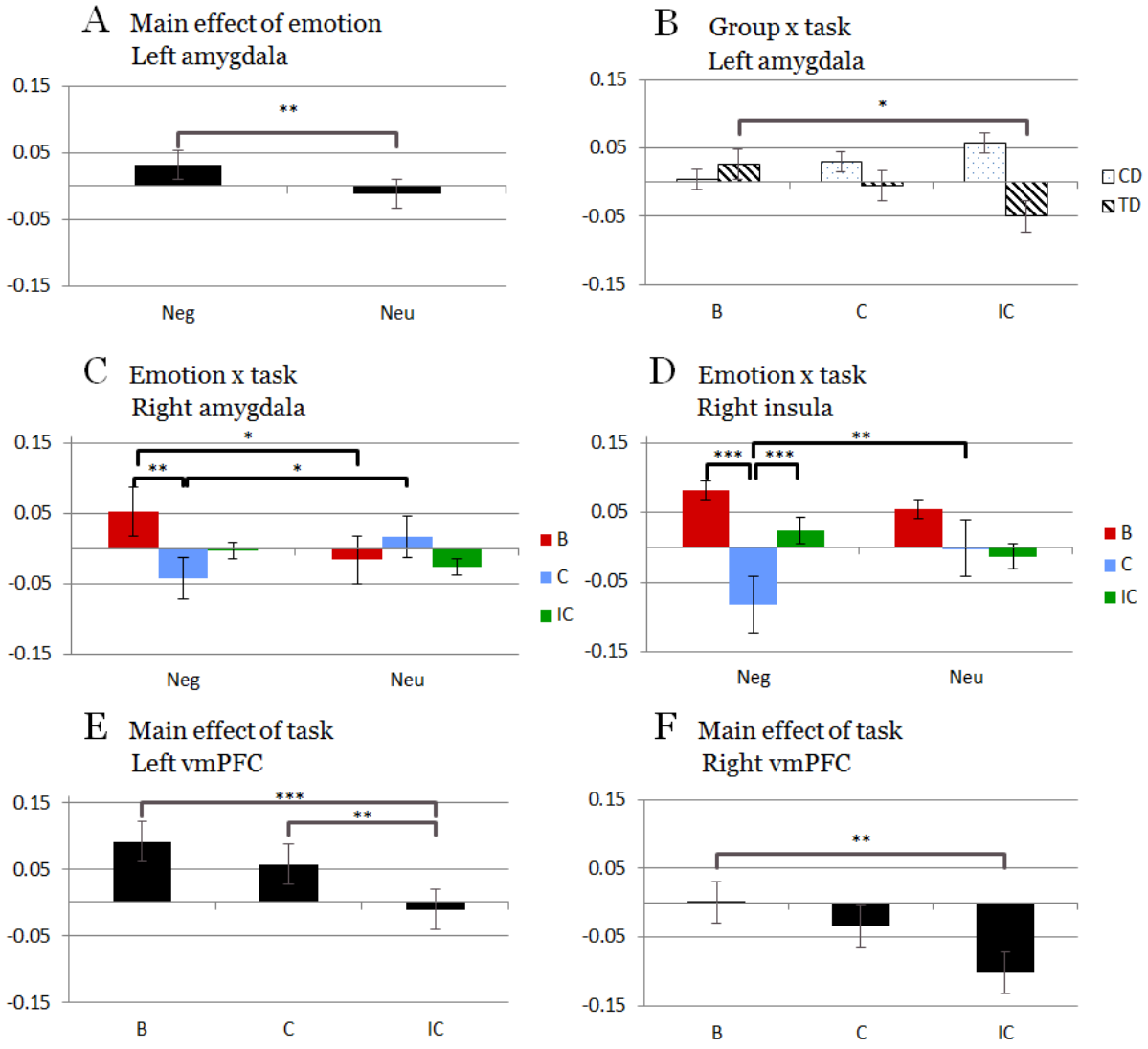

Figure 2 (to be published in color). Bar graphs displaying mean values of parameter estimates (mean centered) in predefined regions of interest (amygdala, insula, ventromedial prefrontal cortex (vmPFC)) for the main effect of emotion and group x task interaction (left amygdala; A/B), emotion x task interaction (right amygdala and insula; C/D), and main effect of task (left and right vmPFC; E/F).

*CD=conduct disorder; TD=typically developing adolescents, *p<.05; **p<.01; ***p<.001, two-tailed t-test; all other t-tests non-significant at threshold p=.05.*

Whole-brain results. Whole-brain analysis of brain activation during affective Stroop task processing revealed significant main effects of *group* and *task* (Table 2), but no significant main effect of *emotion.* There were no significant two- or three-way interaction effects. All images are neurologically displayed using the Multi-image Analysis GUI as available at http://ric.uthscsa.edu/mango/mango.html.

Table 2. MNI coordinates, cluster size and Z-scores for whole-brain results using a FWE cluster level correction of *p*<.05 (cluster building threshold of *p*<.001) for the main effect of *group* and main effect of *task* during the affective Stroop task.

				MNI coordinates		
Brain Region	**Hem**	**k**	**Z_0**	**[mm]**		
				x	**y**	**z**
Main effect of *group*						
CD<TD						
supramarginal gyrus, middle frontal gyrus, including insula and precentral gyrus	R	1035	7.19	40	-10	20
postcentral gyrus	L	392	6.04	-62	-2	26
middle/superior temporal gyrus, hippocampus	R	335	6.66	50	-18	-4
pallidum, thalamus	R/L	309	6.68	16	-16	-2
CD>TD						
inferior/superior parietal lobe, middle temporal/occipital lobe	R/L	4310	6.27	-30	-82	26
precentral gyrus, inferior orbitofrontal lobe, caudate, putamen, including insula	R/L	3869	>8	-30	12	22
rolandic operculum, inferior parietal lobe	L	2545	7.71	-32	-44	-26
inferior/middle/superior frontal lobe, precentral gyrus, insula	R	1680	7.44	48	34	28

lingual gyrus, hippocampus, inferior temporal/occipital lobe, cerebellum	R/L	1114	7.04	32	-54	8
middle/superior frontal gyrus, supplementary motor area, anterior/middle cingulate gyrus	R/L	787	6.28	4	26	44
anterior/middle cingulate gyrus, caudate	R/L	391	6.45	4	-2	32
precentral gyrus, superior frontal gyrus	L	343	6.29	-28	-24	30
inferior parietal lobe, angular gyrus	R	339	5.73	54	-34	18
fusiform gyrus, inferior/middle occipital lobe	L	294	6.00	-46	-82	-8
fusiform gyrus, inferior/middle occipital lobe	R	257	5.81	42	-52	-14
supplementary motor area, superior frontal lobe	L	212	5.78	-18	14	62
Main effect of *task*						
IC>C						
calcarine sulcus, lingual gyrus, superior occipital lobe	R/L	385	4.23	4	-82	0
IC<C						
no suprathreshold voxels						
IC>B						
occipital lobe, fusiform gyrus, calcarine sulcus, cerebellum	R/L	9665	>8	34	-86	0
supramarginal gyrus, inferior/superior parietal lobe, middle/superior frontal lobe	L	4888	>8	-46	-36	58
supramarginal gyrus, inferior/superior parietal lobe	R	1118	5.57	42	-40	52
hippocampus, pallidum, putamen, amygdala	L	791	5.53	-24	0	-8
inferior frontal operculum, precentral gyrus	L	291	5.82	-54	8	38
pallidum, caudate, putamen	R	261	4.74	26	6	-8
IC<B						

middle/posterior cingulate gyrus, paracentral lobule, including precuneus	R/L	1850	5.98	-2	-34	44
inferior/middle temporal lobe, inferior parietal lobe, middle occipital lobe	L	872	6.67	-40	-84	28
middle frontal lobe, precentral gyrus	R	832	4.95	36	-16	44
middle/superior temporal lobe, angular gyrus	R	645	4.65	42	-80	30
inferior temporal lobe, including fusiform gyrus	L	232	4.70	-28	-36	-18
C>B						
supramarginal gyrus, inferior/superior parietal lobe, superior frontal lobe	L	3740	>8	-44	-38	60
cerebellum, occipital lobe, including fusiform gyrus	R	3049	6.71	32	-88	0
cerebellum, occipital lobe, including fusiform gyrus	L	2248	6.99	-38	-90	-8
supramarginal gyrus, inferior/superior parietal lobe	R	747	4.95	44	-40	58
hippocampus, putamen	L	232	4.11	-18	0	14
C<B						
middle cingulate gyrus, precuneus, paracentral lobule	R/L	941	4.96	6	-38	50
postcentral gyrus, precentral gyrus	R	432	4.17	36	-20	56
angular gyrus, middle/superior occipital lobe	L	455	4.81	-44	-82	22
middle/superior temporal lobe	R	312	4.09	64	-52	6
fusiform gyrus, lingual gyrus	R	228	4.48	28	-44	-12
insula, putamen, rolandic operculum	R	221	4.06	36	-12	6

FWE cluster level correction of $p<.05$ (cluster building threshold of $p<.001$)

Hem=hemisphere; k= cluster size; B=blank trial; C=congruent trial; IC=incongruent trial; CD=conduct disorder; TD=typically developing adolescents

Main effect of group. A main effect of *group* (Figure 3) was detected for regions including bilateral parietal and middle/inferior temporal and occipital lobes, bilateral precentral and inferior orbitofrontal areas extending into anterior insula and striatum, frontal cortices, and anterior/middle cingulate cortex (CD>TD) and regions including right middle frontal and supramarginal gyri (extending into posterior insula), left postcentral gyrus, right middle/superior temporal cortex, and bilateral thalamus (CD<TD).

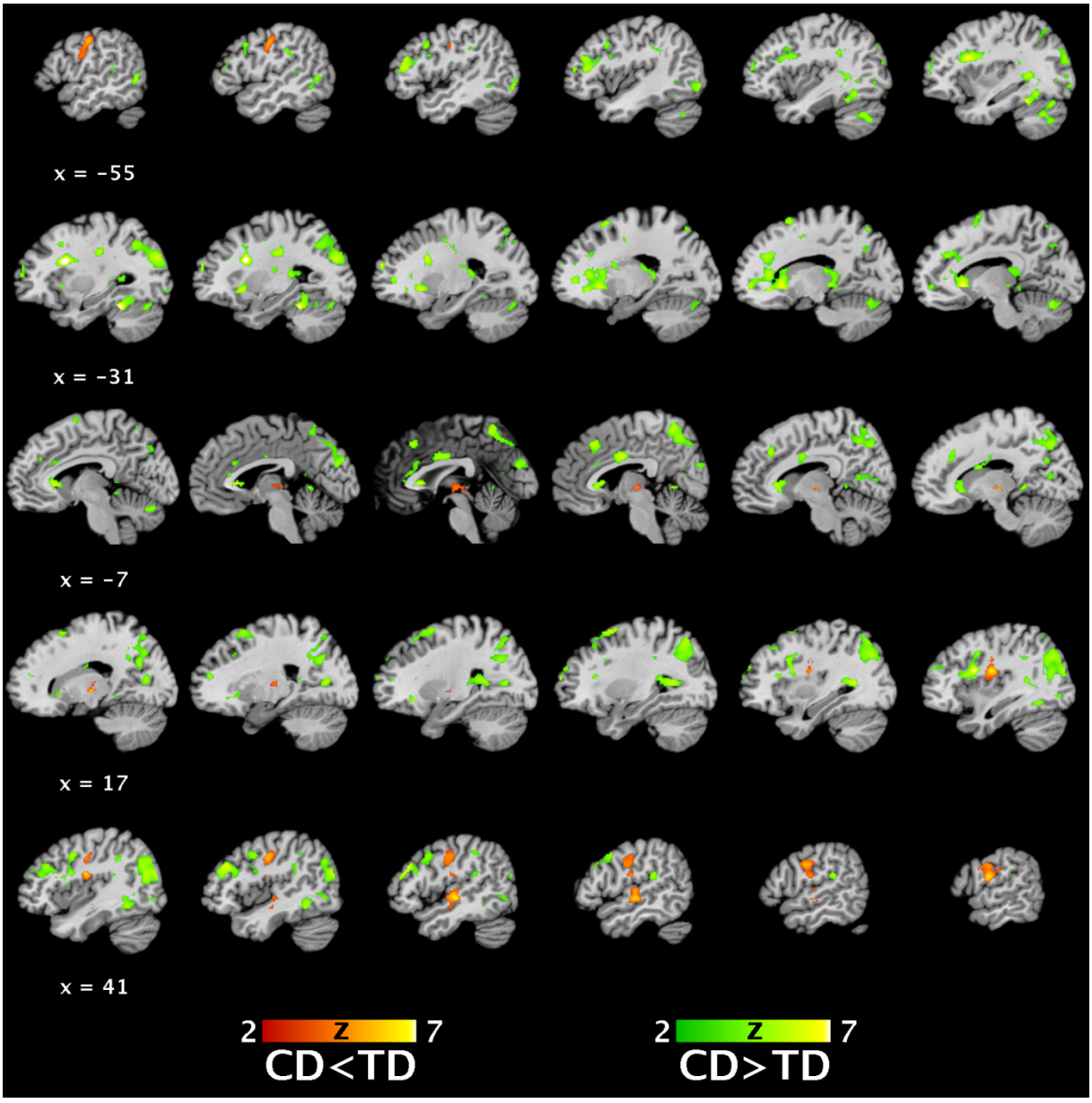

Figure 3 (to be published in color). Statistical parametric maps depicting the main effect of group (masked post-hoc t-tests for group differences in brain activation between conduct disorder (CD) and typically developing (TD) adolescents, 39CD/39TD; hypoactivations in CD in red-yellow, hyperactivations in CD in green-yellow) (p<.05, FWE).

Main effect of task. Regions showing a differential BOLD response in response to *task* included bilateral parietal and frontal lobes, supramarginal gyri, occipital, temporal, and cerebellar regions, right middle cingulate cortex, left precuneus, and left amygdala. Bilateral supramarginal, superior frontoparietal, and occipital areas exhibited increased activity for congruent and incongruent relative to blank trials (IC/C>B). Left amygdala and inferior frontal areas exhibited increased activity for incongruent compared to blank trials (IC>B). In contrast, decreased left inferior parietal lobe, right middle frontal and cingulate cortices, and left precuneus activity was detected for congruent and incongruent relative to blank trials (C/IC<B). Decreased activity in left inferior temporal and right middle/superior temporal regions was related to incongruent versus blank trials (IC<B, SI6).

Discussion

Here we aimed at investigating the interaction of emotion processing and response inhibition in CD youths during an affective Stroop task. ROI analyses revealed a significant *group* x *task* interaction effect reflecting a lack of downregulation of left amygdala activity in response to incongruent task trials for CD compared to TD. This effect was independent of the emotion presented prior to Stroop task performance. Additionally, whole-brain analyses revealed a significant main effect of *group* representing increased anterior insula activity for CD relative to TD regardless of emotion and task demands.

Contrary to our hypothesis and some previous investigations (Euler et al., 2014; Prateeksha et al., 2014; Rubia, Smith, et al., 2009) we did not detect group differences in RTs. However, research has not been conclusive to date and the present finding is in accordance with other studies (Banich et al., 2007; Rubia, Halari, et al., 2010; Rubia, Halari, et al., 2009; Rubia et al., 2008). Increased RTs for neutral compared to negative trials and for incongruent compared to congruent trials were detected across all participants. While increased RTs robustly reflect the Stroop effect (Stroop, 1935), shorter RTs for negative compared to neutral stimuli were not expected. However, participants' responses were more accurate after presentation of neutral relative to negative images. Faster responses at the expense of lower accuracy may be due to heightened stress. Moreover, in line with Rubia, Halari, et al. (2009), CD youths made more errors than TD, which is contrary to other reports in DBD and TD (Banich et al., 2007; Euler et al., 2014; Prateeksha et al., 2014; Rubia, Halari, et al., 2010; Rubia et al., 2008).

In line with our second hypothesis, ROI analyses revealed decreased left amygdala activity during Stroop task trials with a high cognitive load (IC>B) in TD. In contrast, CD youths did not show any downregulation of emotion-related brain areas with increasing task difficulty. Unexpectedly, this group difference was independent of the emotionality. We would have expected to detect a difference depending on the emotion presented (i.e., a downregulation after negative images instead of on any image as observed here). Our data suggests that no task-dependent downregulation of left amygdala response takes place in CD as compared to TD, possibly reflecting altered neuronal functioning of left amygdala which may be linked to altered regulatory processes.

In agreement with the findings presented here, an aberrant amygdala activity in DBD has previously been reported during response inhibition (Hwang et al., 2016), facial emotion processing (Holz et al., 2017; Jones, Laurens, Herba, Barker, & Viding, 2009; Marsh et al., 2008), emotion processing (Sterzer, Stadler, Krebs, Kleinschmidt, & Poustka, 2005), stimulus-reinforcement learning, and reward processing (Finger et al., 2011). In addition to functional MRI evidence, past research has suggested reduced amygdala volumes in adolescents with conduct problems (Fairchild et al., 2011; Huebner et al., 2008; Rogers & De Brito, 2016; Sterzer, Stadler, Poustka, & Kleinschmidt, 2007; Wallace et al., 2014). Together with the findings presented here, evidence thus supports a broader view of the amygdala as a key center of alterations in CD.

Whole-brain results provided further insights into insula activity during the affective Stroop task while distinguishing between insular subdivisions. CD exhibited increased activity in anterior insula implicated in affective and cognitive processing (Chang et al., 2013; Mutschler et al., 2009). Additionally, CD showed decreased activity in posterior insula, an area involved in sensorimotor processing (Chang, Yarkoni, Khaw, & Sanfey, 2013; Mutschler et al., 2009). Our observations are in line with a broader view of the insula in integrating emotion and cognition in healthy adolescents (Chang et al., 2013; Pavuluri & May, 2015), whereas alterations thereof could be hypothesized to reflect an increased allocation of neuronal resources for emotion and cognitive processing, potentially related to a maturational delay in youths with CD. However, the observed differences emerged from a main effect of *group* and therefore need to be interpreted carefully. Future studies shall determine whether right amygdala and insula show significant co-activations (Kober et al., 2008) during task trials following negative stimuli, reflecting on the role of the insula in transferring sensory information to the amygdala (Shelley & Trimble, 2004).

Limitations

For the present study design we used child-appropriate emotional pictures (DAPS; Cordon, Melinder, Goodman, and Edelstein (2013)). However, the short presentation (150 ms) and moderate image valence might have resulted in a reduced impact for CD youths. Moreover, we cannot exclude that confounding factors or comorbidities could have influenced the results. Additionally, the here presented results characterize a group of CD youths on the lower spectrum of CU traits. Interpretation should therefore be drawn with caution. Finally, behavioral and neuronal analyses revealed no three-way interactions (*group* x *emotion* x *task*). This is likely due to the intricate nature of the interaction of emotion processing and response inhibition, which has proven to be very challenging to capture. This is also reflected in earlier studies. For example, a previous study with similar aims neuronally reported a *group* x *emotion* x *task* interaction within the superior frontal gyrus and caudate, however, no such effect was detected in the behavioral analyses (Hwang et al., 2016). Nevertheless, our results are in favor of previous findings of an altered interaction of emotion processing and response inhibition in CD.

Conclusions

We here provide evidence for the neuronal characteristics of the interaction of emotion processing and response inhibition interaction in CD. More specifically, we observed a significant lack of downregulation of left amygdala activity in response to incongruent task trials and increased anterior insula activity for CD relative to TD during affective Stroop task performance. Behaviorally, CD scored significantly lower than TD youths, while reaction times did not differ. While no three-way interactions (*group* x *emotion* x *task*) were detected, our results still support previous findings of an altered interaction of emotion processing and response inhibition in CD. Overall, the present findings extend knowledge on the neurocognitive mechanisms in CD youths and support emotion dysregulation as a core deficit in CD. Future studies shall focus on investigating the interaction of emotion processing and response inhibition in CD subgroups (e.g., variations in callous-unemotional traits, impulsivity, or anxiety).

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Altered neuronal responses during affective Stroop task performance in adolescents with conduct disorder

Supporting information

SI1. Additional information on participants

All adolescents were invited to take part in two separate sessions including psychometric testing and magnetic resonance imaging. Clinical and behavioral assessments were conducted at the Department of Child and Adolescent Psychiatric Center in Basel or at the Department of Psychiatry and Psychotherapy at Charité – Universitätsmedizin Berlin, Campus Mitte, while neuroimaging took place at the University Hospital of Basel or at the Berlin Center of Advanced Neuroimaging at the Charité – Universitätsmedizin Berlin. We excluded subjects with an IQ score below 70. Adolescents with CD were assessed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL, Kaufman et al. (1997) and were excluded if they did not meet the DSM-5 diagnostic criteria for CD.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., . . . Ryan, N. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*(7), 980-988. doi:10.1097/00004583-199707000-00021

SI2. Psychometric testing: Socioeconomic status

Conduct disorder (CD) and typically developing (TD) adolescents did not differ in socioeconomic status as indexed by mothers' education and family income earned within the last 12 months. However, they did differ with regards to fathers' education (U=298.00, p=.017). Furthermore, CD and TD did not differ in subjective social status as assessed by the MacArthur Community ladder measuring social status within their community, but did differ in the MacArthur SES ladder assessing social status within their country (U=196.50, p=.026).

		CD	**TD**	***p***
		[%]	[%]	**Sig. 2-tailed** *Mann-Whitney test*
Mother characteristics				
	N=	28	38	
Education (highest degree earned)	Pre-primary education (ISCED 0)	0.00%	0.00%	.356
	Primary education or first stage of basic education (ISCED 1)	3.60%	2.60%	
	Lower secondary or second stage of basic education (ISCED 2)	14.30%	5.30%	
	(Upper) secondary education (ISCED 3)	60.70%	65.80%	

	Post-secondary non-tertiary education (ISCED 4)	3.60%	5.30%	
	First stage of teritary education (ISCED 5)	17.90%	21.10%	
	Second stage of tertiary education (doctoral level) (ISCED 6)	0.00%	0.00%	
Father characteristics				
	N=	24	37	
Education (highest	Pre-primary education (ISCED 0)	4.20%	0.00%	.017 *
degree earned)	Primary education or first stage of basic education (ISCED 1)	4.20%	0.00%	
	Lower secondary or second stage of basic education (ISCED 2)	4.20%	5,4%	
	(Upper) secondary education (ISCED 3)	62.50%	37.80%	
	Post-secondary non-tertiary education (ISCED 4)	0.00%	2.70%	
	First stage of tertiary education (ISCED 5)	25.00%	54.10%	
	Second stage of tertiary education (doctoral level) (ISCED 6)	0.00%	0.00%	
Family characteristics				
	N=	23	33	
Income earned within the	less than 4'500 CHF	4.30%	3.00%	.224
past 12 months	4500 CHF - 10'699 CHF	4,3%	3.00%	
	10'700 CHF - 15'199 CHF	8,7%	3.00%	
	15'200 CHF - 22'299 CHF	4,3%	3.00%	
	22'300 CHF - 31'249 CHF	8,7%	3.00%	
	31'250 CHF - 44'599 CHF	8,7%	3.00%	
	44'599 CHF - 66'999 CHF	13.00%	12.10%	
	67'000 CHF - 88'999 CHF	8,7%	9.10%	
	89'000 and greater	13.00%	39.40%	
	I don't know	17,4%	6.10%	
	No response	4,3%	15.20%	
		[Mean ± SD]	[Mean ± SD]	
Subjective socioeconomic	*N*=	20	31	
status (MacArthur)	SES Ladder	5.35±2.08	6.68±1.96	.026 *
	N=	21	30	
	SES Comunity ladder	6.57±2.16	7.13±1.78	.346

* p<.05; two-tailed t-test; all other t-tests non-significant at threshold of p<.05

Education ranking according to ISCED97

SI3. Medication of adolescents with CD (*N*=35) and typically developing controls (*N*=39) at MRI session

		CD	TD
		N=35	*N*=39
ADHD medication	Methylphenidate	6	0
	Atomoxetine	1	0
Pain medication	Paracetamol	1	0
Depression/bipolar disorder medication	Quetiapine	1	0
	Valproate	1	0
Allergy medication	Montelukast	0	1
	Antihistamines	0	1

CD=conduct disorder patients; TD=typically developing adolescents

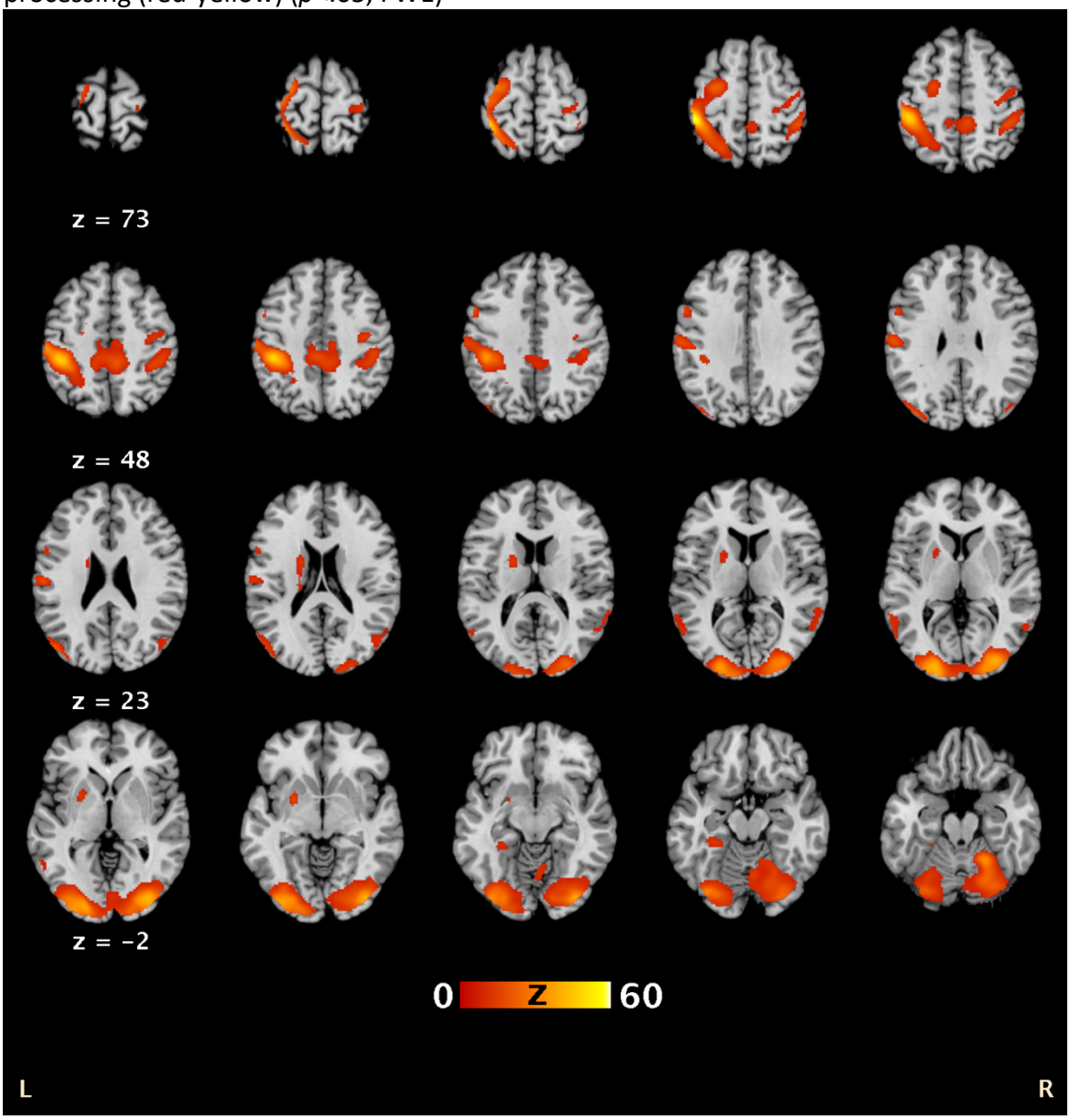
SI4. Button box responses

In the course of the study we faced technical problems with the recording of button #3 of the button box used to record the responses resulting in missing data for six controls and two patients (within the participants included in the present paper) for button number three only. Each file affected by this problem was individually evaluated with regards to whether the missing responses consistently represented correct answers. Only if we were certain that we are able to interpret the missing answers correctly, we proceeded with including the respective file into further MRI analyses (all other data were discarded).

SI5. In-scanner performance (accuracy, reaction times) for adolescents with CD (*N*=39) and typically developing controls (*N*=39)

			CD	TD
			Mean ± SD	Mean ± SD
Reaction times [ms]	Negative prime			
		Congruent	758.8 [98.8]	739.3 [101.3]
		Incongruent	857.9 [115.5]	848.2 [99.3]
	Neutral prime			
		Congruent	767.9 [96.1]	749.0 [99.7]
		Incongruent	872.5 [107.4]	852.2 [111.2]
Accuracy [raw scores]	Negative prime			
		Congruent	46.6 [2.8]	48.0 [2.3]
		Incongruent	43.2 [3.8]	44.8 [3.6]
	Neutral prime			
		Congruent	47.0 [2.9]	48.6 [1.5]
		Incongruent	43.9 [3.6]	45.3 [3.6]

SI6. Statistical parametric maps depicting the main effect of task during affective Stroop task processing (red-yellow) (p<.05, FWE)



Chapter 5 Linking heart rate variability to psychological health and brain structure in female youths with conduct disorder

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Background: Heart rate variability (HRV) is a biomarker for mental/physical health and is predictive of emotion regulation skills. A lower HRV is indicative for a decreased adaptability and is characteristic of conduct disorder (CD). CD individuals with reactive aggression (RA) are more likely to display lower HRV, whereas proactive aggression (PA) is linked to higher HRV. Neuronally, the central autonomic network (CAN: associated areas include the insula, amygdala, hypothalamus, and prefrontal brain regions) has been suggested to regulate HRV. Functional neuroimaging studies have found a link between HRV and areas of the CAN. However, no study has yet directly linked brain structure and HRV.

Objectives: (**i**) assessing HRV in relation to RA/PA (**ii**) investigating brain areas critical for HRV.

Method: We assessed specific aspects of aggressive behavior (reactive-proactive, emotion regulation questionnaire, inventory of callous-unemotional traits) in relation to HRV (respiratory sinus arrhythmia). We performed whole brain regression analysis using HRV as a covariate to investigate a link between brain structure and HRV in girls (15 CD/18 controls).

Results: Preliminary evidence indicates (**i**) a negative correlation between RA and HRV and (**ii**) a negative correlation between HRV and gray matter volume in CAN areas (including prefrontal, cingulate cortex, insula and amygdala; $p<0.001$). Follow-up region of interest analyses were conducted for areas significantly associated with HRV in order to characterize both groups in more detail.

Conclusion: We provide evidence that higher RA is linked to lower HRV, indicative of poor emotion regulation skills, and suggest a connection between HRV and brain structure.

Key Words: heart rate variability, conduct disorder, brain structure

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Chapter 6 General Discussion

The main aim of this thesis was to investigate and further the knowledge about neurobiological correlates of aggression and emotion regulation in children and adolescents. The first aim was to examine the relationship between basal ANS activity and aggression in more detail than has been done before. We therefore included a comprehensive assessment of ANS activity with two measures of general ANS activity (heart and respiration rate) and two measures capturing PNS (heart rate variability) and SNS (pre-ejection period) activity separately, while considering relevant covariates such as smoking. To investigate this aim we followed two distinct analyses approaches: a categorical (chapter 2) and a dimensional approach (chapter 3). In the categorical approach, a standardised psychiatric interview was conducted in order to categorise CD/ODD patients and typically developing children and adolescents. Subsequently, it was investigated whether they differ in ANS activity. In the dimensional approach, individuals with and without a diagnosis were analysed together regarding the relationship between antisocial behaviour dimensions and ANS activity. The second aim of the thesis was to investigate functional brain correlates of implicit-controlled emotion regulation in individuals with and without conduct disorder (chapter 4). The third aim of the thesis was to investigate the relationship between resting HRV and brain structure (chapter 5). In the following sections the main findings, strengths, and limitations of this thesis are discussed. Further, suggestions for future research are presented, followed by a conclusion.

Contrary to our hypothesis, we did not find an inverse relationship between resting heart rate and antisocial behaviour, neither in the categorical nor in the dimensional analysis – which contrasts many previous studies (Latvala, Kuja-Halkola, Almqvist, Larsson, & Lichtenstein, 2015; Murray et al., 2016; Portnoy & Farrington, 2015). This is surprising, considering the statistical power based on a large sample size which tends to result in even small effects to become significant. However, in line with the present findings, a recent meta-analysis reported a trend showing the relationship between low resting heart rate and antisocial behaviour to become weaker with increasing publication year (Portnoy & Farrington, 2015). The effect size reported in this meta-analysis of r=.0995 means that heart rate accounts for variance in the outcome variable of roughly only 1%. In addition to this small effect of resting heart rate, it is not sufficient to consider this measure alone when investigating emotion regulation, as it is influenced by both branches of the ANS. In the dimensional analysis (chapter 3) we found significant, but weak associations between PNS and SNS activity with antisocial behaviour. After controlling for covariates, none of the associations remained significant. In general, our findings of weak ANS associations with psychopathology align with previous research, reporting small to moderate associations (Alvares et al., 2016; Graziano & Derefinko, 2013; Portnoy & Farrington, 2015), with the exception of schizophrenia exhibiting a large effect on HRV (Alvares et al., 2016).

In line with our hypothesis, we found a significantly higher respiration rate in CD patients compared to controls, but only in females (chapter 2). Importantly, the association remained significant after controlling for IQ, medication, smoking and age. This finding has been observed previously in girls with internalising problems (Henje Blom, Serlachius, Chesney, & Olsson, 2014), and in animal aggression research (Carnevali, Nalivaiko, & Sgoifo, 2014). Respiration rate has been neglected as a correlate of human aggression so far, but gains increasing attention for emotional and cognitive processes (Vlemincx et al., 2013; Zelano et al., 2016). Respiration is closely related to HRV and thus influences PNS activity, which our own data confirms by revealing a negative correlation between respiration rate and HRV. Although we did not find significant differences on HRV, respiration rate might nevertheless enhance a certain degree of emotional vulnerability in female CD patients. Anger has been previously linked to a higher respiration rate (Kreibig, 2010). Considering the high loadings on the MAYSI-2 scales 'angry-irritable', this characteristic might contribute to the higher respiration rate. In addition, another aspect based on our subjective impression during the ANS assessment concerns the individuals' reactions to the requirements of the examination: Participants were asked to sit still for 5 minutes which elicited – especially in individuals with CD/ODD – signs of impatience which could be due to traits of impulsivity or irritability. Nearly one third of our female patients exhibits comorbid ADHD – a condition which makes it difficult for the affected individuals to sit still. The suppression of impulses, such as the urge to speak, move, express oneself, might nonetheless affect physiology – a phenomenon which is well known from emotion research when examining the physiological consequences of expressive suppression (Gross, 1998).

Respiration rate is the most accessible of the four ANS parameters we examined, in terms of the degree of influence and control one can exert on it. Thus, respiration rate is a particularly interesting treatment target. For instance, slow breathing, in the range of 6-10 breaths per minute, increases HRV and lowers blood pressure (Russo, Santarelli, & O'Rourke, 2017). The higher HRV might then – according to the neurovisceral integration model – support emotion regulation (Mather & Thayer, 2018) and help to reduce stress and anxiety (Goessl, Curtiss, & Hofmann, 2017).

6.1 CD Subtypes

In accordance with DSM-5 and previous literature (Fanti, 2016), we investigated the impact of aggression subtypes on ANS activity: (1) We included the specifier with limited prosocial emotions (LPE) according to the DSM-5 for identifying a severe subgroup of CD individuals with high CU traits, and (2) internalising disorders to differentiate clinically relevant subgroups. The LPE specifier did not help to identify subgroups with differential ANS activity, such that even those CD patients with high CU traits are not characterized by lower ANS activity. However, the literature on resting ANS activity

and CD with CU traits is scarce, especially concerning the four ANS measures we used in our studies. For instance, lower resting HR was found in a mainly male CD sample (Anastassiou-Hadjicharalambous & Warden, 2008). This association was also reported in middle school students, but only in the male participants (Kavish et al., 2016). Two further studies did not find a link between low HR and CU traits in a sample of male adolescents with DBD (de Wied, van Boxtel, Matthys, & Meeus, 2012) and children with ODD (Wagner et al., 2017), but both studies confirmed a negative association between resting HRV and CU traits. However, in line with our findings, recent studies in CD adolescents detected no incremental value and found limited usefulness of the LPE for subtyping individuals with CD (Colins, 2016; Jambroes et al., 2016). Another investigation showed that children having conduct problems with and without CU traits did not differ in terms of risk for future and stable conduct problems. Instead a multidimensional assessment of psychopathy was more suitable to predict future conduct problems (Colins, Andershed, Salekin, & Fanti, 2018). Thus, a multidimensional model might serve better to subtype CD and to differentiate between more severe groups with potentially distinct physiological profiles. On the other hand, our analysis strategy might have confounded possible effects of CU traits on ANS activity. Specifically, we did not differentiate between subtypes of CD and LPE with versus without internalising disorders. This co-occurrence of both conditions might have veiled a possible impact of CU traits on ANS activity. Research from Fanti and Kimonis (2017) suggests that investigating externalising subgroups with CU traits, but without internalising symptomatology, leads to differential outcomes. For instance, lower heart rate and higher relational aggression was reported in the CU group without internalising problems compared to the CU group with internalising problems.

However, a subgroup of female patients with comorbid internalising disorders showed altered resting ANS activity. In line with our hypothesis, this subgroup exhibited significantly lower HRV compared to CD females without internalising comorbidity, an effect which was absent in males. The lower PNS activity associated with internalising comorbidity is in line with previous findings suggesting higher arousal in this subgroup (Fanti, 2016; Koenig, Kemp, Beauchaine, Thayer, & Kaess, 2016). Assuming that HRV is an indicator of emotion regulation and reflects PFC functioning (Beauchaine, 2015), our finding might question whether CD/ODD per se is actually characterised by emotion regulation deficits. Considering the high prevalence of internalising problems in antisocial and aggressive individuals (Keenan, Loeber, & Green, 1999; Polier, Vloet, Herpertz-Dahlmann, Laurens, & Hodgins, 2012), previous findings on lower HRV in these populations, might have been due to the co-occurring internalising problems. Thus, it might be hypothesised that the alleged emotion regulation problems in CD/ODD are primarily driven by internalising conditions. It is still an open issue to what extent CD/ODD can be characterised by deficient emotion regulation. A recent study investigated this topic using factor analysis (Cavanagh et al., 2017). Their model indicates that emotion dysregulation and ODD can be considered as a single factor, whereas none of the items related to emotion dysregulation

loaded on the CD factor. The authors concluded that ODD is better described as a disorder of emotion regulation, instead of a disruptive behaviour disorder. However, the findings of our event-related fMRI study investigating implicit-controlled emotion regulation (chapter 4) suggest that CD might be characterised by emotion dysregulation. Behaviourally, CD participants performed lower on the affective Stroop task indicated by higher error rates compared to the typically developing participants. On the neural level, they exhibited a lack of downregulation of left amygdala activity during task trials with higher cognitive load and increased anterior insula activity during affective Stroop task performance. Both affected regions are core regions of the CAN (Beissner et al., 2013). Hence, the observed behavioural and neuronal differences might also be associated with HRV, which will be investigated in further studies. In line with the neurovisceral integration model, we found significant associations between HRV and brain structure in both regions (chapter 5). Another relevant aspect for this discussion is the high comorbidity between CD and ODD (Berkout, Young, & Gross, 2011). In our samples the comorbidity ranged from 51.3% (chapter 4) to 64.5% (chapter 2 & 3). Thus, even if ODD might be more strongly related to emotion dysregulation (Cavanagh et al., 2017), the comorbid nature of CD/ODD in the affected individuals renders this distinction less relevant. Accordingly, Blair et al. (2016) posited that CD and ODD are not categorically different, and not associated with distinct neuro-cognitive dysfunctions.

On the other hand it is still open whether HRV reflects emotion regulation abilities and can be considered a marker thereof. An essential question in this context is the magnitude of effects, which are very small – based on recent meta-analyses and our own data. In the case of the most recent and largest meta-analysis (Holzman & Bridgett, 2017), including 123 studies with 14347 participants, HRV explains only 0.81 % of the variance in executive function and emotion regulation tasks. It might be questioned how psychologically meaningful such a small effect essentially is and which role it plays for emotion regulation. A parallel from research on the effect of antidepressants versus placebo might be instructive at this point. Although antidepressants exhibit a statistically significant difference compared to placebo, the difference is so small that it is not detectable by clinicians and thus cannot even be categorised as “minimal improvement”. An important distinction is made here between statistical and clinical significance. Statistical significance helps to ascertain if a real effect – not caused by chance – exists, whereas clinical significance relates to the magnitude of an effect and takes into account if an effect has an impact on an individual’s life (Kirsch, 2016). In the context of research on emotion regulation and ANS activity, “clinical significance” would mean that a notable difference in emotion regulation ability in daily life is observable and significantly linked to ANS activity. Although the stakes in the field of antidepressants are higher – considering the detrimental side effects of antidepressant medication – a rigorous evaluation of the relationships between ANS activity and emotion regulation is warranted. If the assumed connection between physiology and psychological

processes are used as a rationale in therapy, this evaluation becomes even more important. Currently, for instance, an influential theory – the Polyvagal Theory (Porges, 2009) – is used in the context of trauma therapy (Bradshaw, Cook, & McDonald, 2011). If the data suggests that the basic assumptions of this theory are false (Farmer, Dutschmann, Paton, Pickering, & McAllen, 2016; Gourine, Machhada, Trapp, & Spyer, 2016; Grossman, 2016; Grossman & Taylor, 2007; Monteiro et al., 2018), then it might be unethical to continue to use the respective rationale in the treatment of particularly vulnerable patients. The discussion could be opened to the field of psychotherapy as a whole, but is beyond the scope of this thesis. We shortly refer here to an article by Gaab, Blease, Locher, and Gerger (2016), emphasising the need for transparency in psychotherapy to ensure patient autonomy and ethical professional standards.

The notion of HRV as a transdiagnostic biomarker of psychopathology (Beauchaine & Thayer, 2015) becomes particularly interesting when combining independent lines of research. Caspi et al. (2014) identified a General Psychopathology dimension, called the p factor, which might explain psychiatric disorders better than the conventional three order factor structure. At the peak of severity of the p factor, schizophrenia is located. Interestingly, this condition shows a large effect size linked to HRV (Alvares et al., 2016). Thus, these lines of evidence might suggest some validity for the notion of HRV as a transdiagnostic biomarker of psychopathology, paralleling the severity of the p factor. However, we have not detected a significant relationship between HRV and CD which could suggest a location at the lower end of severity of the p factor. In contrast, the female CD group with internalising disorders might exhibit a higher p level which tends to be characterised by comorbidities (Caspi et al., 2014), and is therefore associated with significantly lower HRV than the female CD group without internalising comorbidity. Additionally, a methodological aspect might contribute to the null findings in the CD patients. Our study in chapter 4 – where we observed an impact of affective and cognitive stimulation on neuronal activity – suggests that it might be insufficient to merely investigate resting conditions which we used in our ANS studies (chapter 2 & 3). Thus, the investigation of ANS reactivity – elicited for instance by emotion evocation – might reveal differences in ANS activity between aggressive and non-aggressive individuals, with and without CU traits (Beauchaine & Thayer, 2015; de Wied et al., 2012; Fanti, 2016; Graziano & Derefinko, 2013).

6.2 Physiological Phenotypes

A further aim was to examine if ANS measures might be suited to create empirically based groups, as opposed to groups based on arbitrary diagnostic criteria. This biologically-informed approach aligns partially with the RDoC framework. A high and a low arousal cluster for boys and girls arose from our analysis. As mentioned above, previous research would suggest differential associations to

psychopathology for these patterns, e.g., internalising symptoms being related to higher ANS activity, and callous-unemotional traits being linked to lower ANS activity (Fanti, 2016). Our data does not provide evidence for such associations. In conclusion, also the reversed approach of creating groups of individuals based on resting ANS activity does not account for substantial variance in antisocial behaviour and comorbid psychopathology. The finding that patients were equally distributed over both clusters highlights the limited value for classifying individuals based on baseline ANS measures. However, alternative analysis approaches based on ANS measures might reveal groups with elevated psychopathology. For instance, non-reciprocal activation of both ANS branches, id est, either concurrent activation or inhibtion of the SNS and PNS, has been positively linked to externalising behaviour in the context of marital conflict (El-Sheikh et al., 2009). Thus, a specific screening of individuals with non-reciprocal ANS activity could possibly identify groups with higher levels of psychopathology.

6.3 HRV and Brain Structure

Based on the scarce literature and the neurovisceral integration model, we hypothesised to find associations between resting HRV and brain structure in CAN regions (including the insula, amygdala, hypothalamus, brain stem and frontal brain regions). In line with our hypothesis, we found significant correlations in the whole brain analysis between HRV and gray matter volume indices in areas associated with the CAN, namely the amygdala, insula, right cingulate/medial PFC and the left inferior and bilateral middle OFC. Some of these findings are in line with previously identified regions in adults, such as the cingulate/medial PFC (Winkelmann et al., 2016; Wood et al., 2017; Woodward et al., 2008; Yoo et al., 2018) and the OFC (Yoo et al., 2018). Notably, our findings also confirm that predominantly the right and not the left cingulate cortex is associated with HRV, which is evident in the other studies. This might suggest a particular role of the right cingulate cortex for the central control of heart rate and its variability (Winkelmann et al., 2016). Additionally, we also found significant negative correlations between HRV and gray matter volume in the insula and amygdala which have not been reported before. However, in the literature on functional brain correlates, HRV has been associated with the activity in the amygdala and the insula. For instance, positive correlations were reported between HRV and cerebral blood flow in the left amygdala and insula during a working memory task (Gianaros, Van der Veen, & Jennings, 2004). In contrast to the findings in adults, all our correlations between HRV and brain structure are negative, which has also been recently found in one study in healthy female adolescents (Koenig et al., 2017). These findings warrant further research investigating the potential influence of age on the relationship between HRV and brain structure.

Although, in one study a clinical sample was included, indicating no impact of the presence of emotional problems on the association between HRV and brain structure (Woodward et al., 2008), we found differences in the associations between CD patients and typically developing youths. Whereas in our post-hoc region of interest analysis the gray matter volume of the insula and the right cingulate/medial PFC were negatively correlated with HRV in both groups, the amygdala was only found in CD patients and the left inferior and bilateral middle OFC only in healthy individuals to be negatively associated with resting HRV. Neuroimaging studies have repeatedly linked aggressive behaviour in youths to structural and functional amygdala alterations (Raschle et al., 2015), which we also confirmed in our own fMRI study (chapter 4). Our study showed for the first time a relationship between HRV and the gray matter volume of a sub-cortical region, which we only found in aggressive adolescents and might therefore be a specific finding for this group.

6.4 Covariate Smoking and Emotion Regulation

Findings regarding the covariate smoking should be considered further. The positive association between smoking and antisocial and comorbid psychopathology is in line with prior research (Jennings et al., 2013; Pagani et al., 2017; Talati, Keyes, & Hasin, 2016). Smoking influences both ANS and brain functioning. Thus, it might be an important confounding factor in the neurobiological research on aggression and emotion regulation. The influence on ANS activity is reflected by lowered PNS and enhanced SNS activity (Dinas, Koutedakis, & Flouris, 2013) – which is in accordance with our own data – and might thus impair emotion regulation. Brain development is significantly impacted by smoking, which causes the ingestion of a host of neurotoxins, and is linked with a disruption of brain regions implicated in olfaction, executive functioning and emotion regulation (Fagundo et al., 2015; Pagani et al., 2017; Swan & Lessov-Schlaggar, 2007). Smokers exhibit functional and structural alterations in brain regions important for emotion regulation, such as multiple PFC regions, the ACC, insula and amygdala (Sutherland et al., 2016; Tang, Tang, & Posner, 2013; Vňuková, Ptáček, Raboch, & Stefano, 2017; Zhou et al., 2017). The affected regions are part of the CAN, and overlap with regions where we found HRV and brain structure relationships (chapter 5). Further, in our study on implicit emotion regulation, we found functional differences in these brain regions between CD patients and controls (chapter 4). Interesingly, implicit emotion regulation has been shown to be impaired in smokers who use frequently expressive suppression (Fucito, Juliano, & Toll, 2010), which is considered an unhealthy emotion regulation strategy (John & Gross, 2004). Expressive suppression has also been associated with earlier smoking initiation (Magar, Phillips, & Hosie, 2008) and years of smoking (Fucito et al., 2010). We have not controlled for smoking in the fMRI sample, but in the ANS samples. CD patients have a much higher average of smoked cigarettes per day, more than 20 times higher in females compared to controls. Studies indicate associations, even in the form of passive smoking, with CD,

ADHD and internalising disorders (Bandiera, Richardson, Lee, He, & Merikangas, 2011). Hence, the negative impact of smoking on emotion regulation, emotion regulation strategy as well as their neurobiological basis, suggests that associations between CD, ANS and neural correlates of emotion regulation might possibly be confounded by smoking.

Furthermore, smoking has been related to olfactory dysfunction (Ajmani, Suh, Wroblewski, & Pinto, 2017), which is negatively associated with executive functioning (Fagundo et al., 2015). Interestingly, nasal respiration entrains neural oscillations in brain regions, such as the olfactory cortex, the amygdala and hippocampus. In accordance with the affected brain regions, better fear discrimination and memory retrieval have been linked to nasal inspiration, compared to the oral route of respiration (Zelano et al., 2016). Based on the disrupted brain regions associated with smoking, it might be hypothesised that smoking obstructs the impact of nasal respiration on brain activity in regions implicated in emotional and cognitive processes. Thereby, respiration might exert less modulatory influence on these processes. The entrainment of neural oscillations through respiration is one hypothesised way by which HRV and concurrently emotion regulation are enhanced (Mather & Thayer, 2018). In this light, smoking bears direct relevance in the context of the neurovisceral integration model and the investigation of the interaction between the ANS and the brain.

6.5 Strengths

One major strength of this dissertation is the inclusion of a wide array of neurobiological correlates of aggression and emotion regulation, ranging from multiple parameters of the ANS, together with a multitude of covariates, to functional brain correlates as well as the interaction between the brain and the heart. Further, on a behavioural level, we used a variety of self-report as well as diagnostic interview data and an assessment of implicit emotion regulation with an event-related fMRI task. This multilevel analysis using different approaches, as well as the biomarkers we included, align partially with concepts of the RDoC framework (Beauchaine, 2015; Beauchaine & Thayer, 2015). We studied those aspects with respect to sex (chapter 2 & 3) using a large international sample including data acquired across seven European countries and containing not only healthy adolescents, but additionally those with clinically significant levels of aggressive and antisocial behaviour. Thus, we were able to capture the full spectrum of antisocial behaviour – from very low to very high. This wealth of data assessed in this difficult to recruit population allowed us to apply two distinct analysis approaches on the same sample: a categorical and a dimensional approach. Increasing evidence suggests the necessity to include dimensional constructs – as proposed in the RDoC framework – in order to investigate mental health and its relationship to neurobiology, as categorical classifications based on DSM and ICD are of limited validity.

6.6 Limitations

One important limitation (chapter 2 & 3) consists in using baseline ANS measures only. Growing evidence highlights the importance of ANS reactivity for adaptive functioning (Graziano & Derefinko, 2013). It is possible that we would have found associations between ANS activity and antisocial behaviour if we had included ANS reactivity measures in our analyses (e.g., HRV changes to stress or in response to aversive stimuli). Second, we have not specifically investigated the impact of alcohol and substance use disorders in all our analyses, which could have influenced results, since both are altering ANS and CNS activity (Lisdahl, 2013; Lubman, Yücel, & Hall, 2007; Quintana, McGregor, Guastella, Malhi, & Kemp, 2013; Silveri, Dager, Cohen-Gilbert, & Sneider, 2016). Besides the above mentioned limitations for the study on neural correlates of implicit emotion regulation (chapter 4), we have not controlled for the influence of smoking which – as outlined above – could be a confounding factor in the study of the neurobiology of aggression and emotion regulation. The same limitation also applies for our study on HRV and brain structure (chapter 5). In addition, we only used HRV and no other ANS measure for this analysis. On the one hand, this could have influenced the results as the respiration rate is closely related to HRV (Grossman & Taylor, 2007). On the other hand, we cannot examine which role other ANS measures play for the relationship between ANS activity and brain structure. For instance, in a recent study the negative association between SNS activity and the left mPFC was reported (Wood et al., 2017). Finally, in the study of chapter 5, we used a small sample, which restricts the generalisability of our findings.

6.7 Future Research

Considering the close relationship between smoking and respiration rate, at least in females, it would be worthwhile to include other respiratory variables in future studies (e.g., tidal volume, variability, pCO2), as they have been related to internalising problems which are of direct relevance to the study of antisocial behaviour. As mentioned above, increasing research on respiration and HRV might open the door for the inclusion of this knowledge in treatment methods and foster the progress of new or complementary treatment approaches. Considering the strong relationship between antisocial behaviour and smoking and its relevance to the neurobiology of emotion regulation, we recommend to assess smoking routinely in studies of ANS, CNS and aggressive and antisocial behaviour. Ideally, it should be assessed as a continuous variable, given its non-linear relationship to pre-ejection period (Hu et al., 2017), allowing a more informative analysis. In the context of developmental research on aggression and antisocial behaviour it might be even more important – considering the impact of smoking on neurodevelopment. Contrasting findings on the associations between HRV and brain structure in adult compared to adolescent samples, warrant the investigation of developmental

aspects regarding heart-brain connections in longitudinal studies. Further, the neurovisceral integration model posits a link between the neural underpinnings of emotion regulation and HRV. Thus, future studies on the neural correlates of emotion regulation could include HRV to evaluate this posited relationship further. To allow a more comprehensive understanding of the interaction between the ANS and the CNS, future research should include several ANS measures to assess if, for instance, HRV figures as prominently in this interaction as assumed in this neurovisceral integration model. As mentioned above, reactivity measures might reveal a stronger link to aggression and emotion regulation. As opposed to baseline measures in an artificial laboratory study environment, a more ideal assessment of the ANS emotion regulation association would be in daily life interactions (Verkuil, Brosschot, Tollenaar, Lane, & Thayer, 2016). Thereby, when an individual acts aggressively, which can be considered as failed emotion regulation depending on the context, it could be examined if a change in ANS activity, notably in PNS, occurs before and/or during the act. As HRV is suggested to index PFC functioning (Beauchaine & Thayer, 2015) and PFC dysfunction is related to aggression, it might be hypothesised that HRV changes precede or accompany the aggressive act. To approximate daily life interactions, virtual reality environments could be used. This approach also insures an adequate level of laboratory standardisation while increasing ecological validity (Van Gelder, Otte, & Luciano, 2014). The combination of virtual reality methods with neurobiological markers in research on aggression has also been proposed by Cornet (2015).

6.8 Conclusion

The findings presented in this dissertation advance the knowledge on neurobiological correlates of aggression and emotion regulation in children and adolescents. In line with recent evidence, our studies suggest, that resting ANS activity, especially heart rate, might not be as strongly correlated with antisocial behaviour as previously assumed. In addition, the novel finding of higher respiration rate in female CD suggests that this measure might be an important variable that should be further considered in future research – with a particular focus on its potential to impact HRV and emotion regulation. Thus, more research on respiration in vulnerable individuals could improve current treatment modalities. Further, the result indicating that comorbid internalising disorders influence HRV in female CD patients warrants additional investigation and consideration of specific treatment needs. Patients with CD and comorbid internalising problems might represent a more severe psychopathological subgroup, possibly reflected by a higher p factor (Caspi et al., 2014). Correspondingly, HRV might function as a transdiagnostic biomarker of psychopathology and emotion regulation problems. On the other hand, it should be emphasised that all associations between psychological and physiological processes should be interpreted with caution. The small effects which we and others found, question the relevance of resting ANS measures as indicators or markers of

psychological processes, such as emotion regulation. Additionally, the fact that we only found these associations in the categorical analysis, warrants further scepticism and highlights the importance of methodological considerations in psychophysiological studies. In line with this scepticism, our results of the biologically-informed approach highlight the limited value for classifying individuals based on baseline ANS measures. However, our findings of the neural correlates of implicit emotion regulation additionally support the notion of CD being characterised by deficient emotion regulation. Behaviourally, CD participants performed lower on the affective Stroop task indicated by higher error rates compared to the typically developing participants. On the neural level, they exhibited a lack of downregulation of left amygdala activity during task trials with higher cognitive load and increased anterior insula activity during affective Stroop task performance. This study suggests the relevance of investigating physiological processes in the context of emotional stimulation, as opposed to only using neutral resting conditions. Thus, ANS reactivity measures might reveal meaningful associations with aggression in further studies. Moreover, we reported a link between resting HRV and brain structure in CAN regions, which are involved in emotion regulation. Overall, we followed the suggestion to interpret ANS findings in a CNS framework, supported by the neurovisceral integration model as well as the RDoC framework (Beauchaine, 2015; Beauchaine & Thayer, 2015). Finally, we highlighted the relevance of smoking for emotion regulation which has been neglected so far in the context of neurobiological research on aggression and might be an important confounding factor to consider in future studies.

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Declaration by Candidate and Publication List

I hereby declare that this dissertation was prepared independently. The three research articles have been published or submitted to peer-reviewed journals and were written in collaboration with the listed co-authors. All citations are specified and only the mentioned sources were used in this dissertation.

The following articles are included:

Article 1

Oldenhof, H. *, **Prätzlich, M.** *, Ackermann, K., Baker, R., Batchelor, M., Baumann, S., . . ., Stadler, C., Popma, A. (2018). Baseline autonomic nervous system activity in female children and adolescents with conduct disorder: psychophysiological findings from the FemNAT-CD study. *Journal of Criminal Justice.*

Article 2

Prätzlich, M.*, Oldenhof, H. *, Steppan, M., Jansen, L., Raschle, N.M., Kersten, L., …, Popma, A., Stadler, C. (2018). Resting autonomic nervous system activity is unrelated to antisocial behaviour dimensions in adolescents: Cross-sectional findings from a european multi-centre study. *Journal of Criminal Justice.*

* shared first authorship

Article 3

Fehlbaum, L. , Raschle, N., Menks, W.M., **Prätzlich, M.**, Flemming, E., Wyss, L., Euler, F., Sheridan, M, Sterzer, P., Stadler, C. (submitted). Altered neuronal responses during affective Stroop task performance in adolescents with conduct disorder. *Frontiers in Psychology.*

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Extra contribution

Prätzlich, M., Raschle, N.M., Fehlbaum, L.V., Menks, W.M., Kersten, L., Mannstadt, S., Dietrich, C., Stadler, C. (2016). Linking heart rate variability to psychological health and brain structure in female youths with conduct disorder. 5th edition of the EFCAP congress, Porto, Portugal; 05/2016.

Additional Artcicles related to the Topic of this Dissertation:

Kohls, G., Baumann, S., Gundlach, M., Scharke, W., Herpertz-Dahlmann, B., Blair, R.J., **Prätzlich, M.**, ... Stadler, C., & Konrad, K. (in preparation). Emotion dysfunction in girls and boys with conduct disorder.

Kersten, L., Vriends, N., Steppan, M., Raschle, N. M., **Prätzlich, M.**, Oldenhof, H., ... & Stadler, C. (2017). Community Violence Exposure and Conduct Problems in Children and Adolescents with Conduct Disorder and Healthy Controls. *Frontiers in Behavioral Neuroscience*, 11, 219.

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