Universität Basel

Fakultät für Psychologie

# Emotion processing deficits in youth with conduct disorder and youth with autism spectrum disorders: Potential transdiagnostic factors and neurobiological correlates

**Inauguraldissertation** zur Erlangung der Würde einer Doktorin der Philosophie vorgelegt der Fakultät für Psychologie der Universität Basel von

**Antonia Tkalcec**

aus Offenbach am Main, Deutschland

Basel, 2023

Universität Basel

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2. Tkalcec A.*, Bierlein M.*, Seeger-Schneider G., Walitza S., Jenny B., Menks W. M., Felhbaum L. V., Borbas R., Cole D. M., Raschle N., Herbrecht E., Stadler C.† & Cubillo A.† (2023). Empathy deficits, callous-unemotional traits and structural underpinnings in autism spectrum disorder and conduct disorder youth. Autism Res. Aug 7. doi: 10.1002/aur.2993. Epub ahead of print. PMID: 37548142.

   *Shared first authorship

   † Shared last authorship

3. Tkalcec A., Baldassarri A., Junghans A., Somasundaram V., Menks W. M., Fehlbaum L. V., Borbàs R., Raschle N., Seeger-Schneider G., Jenny B., Walitza s., Cole D. M., Sterzer P., Santini F., Herbrecht E., Cubillo A.† & Stadler C.† (2023). Gaze behavior, facial

emotion processing and neural underpinnings: A comparison of adolescents with autism spectrum disorder and conduct disorder. Submitted for publication.

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3. Preregistration: ☐ ja ☒ nein
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   Open-Access-Data/Analyse: ☐ ja ☒ nein
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Ort, Datum Basel, 26.09.23

Signatur A. T

Vorname Nachname Antonia Tkalcec

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## *Abstract*

Many disorders exhibit impairments in emotion processing. Yet, studies investigating potentially shared and disorder-specific deficits at the behavioral and neural levels are lacking. The main aim of this study is thus, to compare two disorders showing emotion processing deficits, conduct disorder (CD) and autism spectrum disorder (ASD). Moreover, in CD and ASD, emotion processing deficits are detectable early in life. These include reduced attention to the eye region during facial emotion processing and high prevalence rates of co-occurring callous unemotional (CU) traits. Focusing on these as potential transdiagnostic factors for emotion processing deficits might help to gain deeper knowledge on the shared and disorder specific deficits.

The main aim of this thesis is to explore the potential transdiagnostic contribution of atypical eye gaze and co-occurring CU traits at the behavioral and neural level for emotion processing impairments often described in youth with CD and youth with ASD. The second aim was to investigate whether heart rate variability (HRV) influences generic self-regulation or specifically emotion regulation abilities and underlying neural structures in youth with CD compared with typically developing peers (TD). For this, we analyzed gaze behavior during an implicit facial emotion processing paradigm and functional Magnetic Resonance Imaging (MRI). Then, the impact of CU traits on empathy abilities were investigated using psychometric measures of empathy and structural imaging data. Finally, we analyzed the association between baseline HRV indices and task performance during an emotional go/no-go paradigm using data from the multicentered FemNAT-CD project.

The findings of the first study suggest that while reduced eye gaze and differences in brain activation may be disorder specific, atypical gaze patterns may be transdiagnostic. In the second study, CU traits have shown both transdiagnostic and disorder specific influences which may partially depend on the disorder, the type of emotion processing and the neural correlate investigated. Thus, gaze behavior and CU traits, although expressed in a disorder specific way, are shown in CD and ASD and impact emotion processing in both disorders. The third study suggests that HRV may be an indicator for potential self-regulation deficits in youth with CD and TD.

In sum, this thesis provides evidence for a transdiagnostic and disorder-specific impact of early indicators atypical emotion processing. More studies are needed to explore and compare the underlying mechanisms of atypical gaze patterns and subdimensions of CU traits in disorders with emotion processing deficits. This may help to better understand the disorder specific focus of impairment and to develop tailored treatment options.

# *1. Introduction*

## 1.1 Early development of emotion processing

The ability to process emotions is crucial for successful interactions and entails multiple subprocesses such as emotion recognition and emotion regulation which begin to develop in the first years of life. Soon after birth, infants develop a preference for human faces and facial expressions which enables social interactions and social bonding (Bastianello et al., 2022; Csibra & Gergely, 2006; Morton & Johnson, 1991; Quinn et al., 2019).

Processing of facial expressions is a complex process including the perception, recognition, and interpretation of facial expressions fundamental for social interactions (Carnevali et al., 2022; Quinn et al., 2019). Moreover, the facial features important to discriminate between facial expressions are the eye and mouth regions (Lee & Anderson, 2017; Schyns et al., 2007). More specifically, fixating on the eye region is crucial for the accurate processing and recognition of emotional facial expressions (Adams & Kleck, 2003; Frischen et al., 2007; Pellicano & Macrae, 2009; Schindler & Bublatzky, 2020). Reduced fixation to the eye region has been linked to impairments in socio-emotional development in the first years of life (Johnson et al., 2005) and to other related deficits such as empathic responses and theory of mind (ToM) processes (McCrackin & Itier, 2021; Warnell et al., 2022). Interestingly, fixating on the eyes has been linked to more empathy and higher abilities to read emotional states and emotion recognition (Baron-Cohen, 2000; Besel & Yuille, 2010; McCrackin & Itier, 2021; Warnell et al., 2022). This has been termed as the "empathic gaze" (Cowan et al., 2014) and leads to suggestions of a strong association between trait empathy and directed eye gaze during facial processing highlighting the importance of gaze in social and emotional functioning. As proposed in the process theory of emotion regulation (J. J. Gross & Thompson, 2006), attention is an important step towards an accurate recognition of and regulated response to emotional stimuli. The model states that an emotional response to emotional stimuli is based on 3 preceding steps: (1) exposition to a situation; (2) attention to a particular aspect of the situation; and (3) interpretation of the situation or appraisal. Given that developmental changes do not stop after childhood but are particularly prominent during adolescence (McLaughlin et al., 2015), a main focus of this thesis is the attention to social cues and emotional response to emotional stimuli in adolescence.

## 1.2 Adolescent development of emotion processing

A particularly sensitive developmental period are the years of adolescence, including widespread changes in emotion processing that manifest at different levels. Among others, these developmental changes involve psychological, neurobiological, and physiological domains (McLaughlin et al., 2015). During adolescence, these different domains form complex and interrelating trajectories relevant to the development of different psychopathologies (McLaughlin et al., 2015). Many psychopathologies emerge in adolescence (Kelly et al., 2015; Powers & Casey, 2015; Ullsperger & Nikolas, 2017; Zahn-Waxler, Shirtcliff, & Marceau, 2008). Hence, it is not surprising that researchers have shown increased interest in different domains and psychopathologies in adolescence in the last few decades. Importantly, deficits in emotion processing have been suggested to constitute a liability spectrum underlying many psychopathologies (Kret & Ploeger, 2015). Disorders often displaying disruptions in emotion processing are, for instance, conduct disorder (CD) and autism spectrum disorders (ASD) among others (Kret & Ploeger, 2015; Marsden et al., 2019; McTeague et al., 2020). However, if these deficits are shared or disorder specific has so far been scarcely investigated.

## 1.3 Atypical development of emotion processing in conduct disorder and autism spectrum disorders

The available evidence suggests that youth with CD and youth with ASD show emotion processing deficits in emotion recognition, emotion regulation and empathic abilities (Fairchild et al., 2009, 2019; Harmsen, 2019; Martin-Key et al., 2017; Reyes et al., 2019; Stevens et al., 2001; Yeung, 2022). This suggests a potential overlap in emotion processing deficits. However, what if these potential overlaps are linked to specific early indications of emotion processing deficits present across disorders with emotion processing deficits hence, function as transdiagnostic factors? For instance, an early indicator for emotion processing impairments often described in CD and ASD is the attention to social cues in facial expressions (Johnson et al., 2005, 2015).

### 1.3.1 Facial emotion processing deficits in conduct disorder

CD is characterized by aggressive and antisocial behavior that violates the rights of others or major age-appropriate societal norms or rules but also bullying others, vandalism, lying, and stealing (American Psychiatric Association, 2013). For youth with CD however, deficits have been described in the processing of facial expressions through reduced eye gaze (Bours et al., 2018; Menks et al., 2021) and also empathy processes (J. Blair, 2013; R. J. R. Blair et al., 2014;

Igoumenou et al., 2017). Yet, how these deficits are linked to the mechanisms underlying gaze behavior are still unclear.

#### *1.3.1.1 Impact of eye gaze*

In recent studies, youth with CD have shown less attention to the eye region compared to controls especially for negative or threatening facial expressions (Bours et al., 2018; Martin-Key et al., 2017; Menks et al., 2021). However, given that CD is a heterogeneous disorder represented by several different symptom profiles and etiologies (Burt, 2012; Clanton et al., 2017; Fairchild et al., 2019; Nock et al., 2006; Van Goozen et al., 2007), reduced eye gaze was most consistently found for those with CD and co-occurring callous unemotional (CU) traits (Bedford et al., 2015, 2017; Billeci et al., 2019; Ciucci et al., 2015; Dadds et al., 2006, 2008; Demetriou & Fanti, 2022; Huffman & Oshri, 2022; Levantini et al., 2022; Martin-Key et al., 2017; White et al., 2016; Woodworth & Waschbusch, 2008). It has been hypothesized that low eye contact with the mother in early childhood (Bedford et al., 2015, 2017) might be a precursor for subsequent development of CU behaviors and traits. Furthermore, adolescents with CU traits also show low attention to the eye region in facial expressions (Bedford et al., 2015, 2017; Billeci et al., 2019; Ciucci et al., 2015; Dadds et al., 2006, 2008; Demetriou & Fanti, 2022; Huffman & Oshri, 2022; Levantini et al., 2022; Martin-Key et al., 2017; White et al., 2016; Woodworth & Waschbusch, 2008). Thus, low eye gaze might be linked to CU traits and facial emotion processing deficits which, moreover, raises the question of CU traits' impact on these deficits.

#### *1.3.1.2 Impact of callous unemotional traits*

Individuals with co-occurring CU traits represent a distinctive phenotype of CD (American Psychiatric Association, 2013). Children and adolescents with high CU traits display particularly severe and persistent conduct problems, aggression, antisocial behaviors, and delinquency (Frick et al., 2014; Frick & White, 2008; Kimonis et al., 2008) and are at greater risk for worse prognosis and poorer treatment response (Frick et al., 2014, 2018; Pisano et al., 2017). As such, CU traits are included as a specifier labeled with "Limited Prosocial Emotion" in the diagnosis of CD in The Fifth Edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5; (American Psychiatric Association, 2013)). This phenotype is defined by a lack of empathy, guilt and shallow affection (Frick & Morris, 2004) and can be already assessed in children from the age of 2 years (Kimonis et al., 2016). The available evidence also suggests that emotion processing deficits might play a significant role in the development of CU traits (R. Blair, 2015; Frick & Viding, 2009). Apart from reduced eye gaze, studies have focused on specific features of CU traits such as a lack

of empathy. Empathy is defined as the ability to feel and understand the emotions felt by another person (Eisenberg et al., 2013) and deficits in empathy abilities could potentially have significant effects on social functioning throughout life (Findlay et al., 2006; Jolliffe & Farrington, 2004; Stern & Cassidy, 2018). Based on research, the main aspects of empathy are affective empathy (sharing an emotion of another) and cognitive empathy (understanding the feelings and perspectives of another) (Shamay-Tsoory & Aharon-Peretz, 2007). Research suggests that those with high CU traits mainly show deficits in affective empathy deficits rather than cognitive empathy (Jones et al., 2010; Waller et al., 2015). However, findings of a recent meta-analysis suggest that CU traits are similarly linked to both empathy aspects (Waller et al., 2020). Taken together, the presence of CU traits may be particularly strong indicator for some emotion processing deficits in CD. Yet, their underlying neural mechanisms are still unclear.

#### *1.3.1.3 Neural findings*

Reduced eye gaze has been suggested to be associated with the facial processing deficits linked to amygdala and anterior insula (AI) hypoactivity (Dadds et al., 2008, 2014; Menks et al., 2021). In addition, CU traits have also been linked to reduced brain activation in amygdala and anterior cingulate (ACC) when presented with negative facial expressions such as fearful or sad faces (Aggensteiner et al., 2022; Jones et al., 2009; Marsh et al., 2008; Szabó et al., 2017). Thus, impairments in facial emotion processing might be caused by differences in eye gaze. Brain structural findings in youth with CD have also shown reduced gray matter volume (GMV) in the ACC, ventromedial prefrontal cortex (vmPFC) and AI (Fairchild et al., 2019; J. C. Rogers & De Brito, 2016; Sebastian et al., 2016). These brain regions have been linked to different empathy processes. While the ACC has been linked to affective empathy processes (Bernhardt & Singer, 2012; Bzdok et al., 2012; Lamm et al., 2011), the vmPFC and AI are involved in processes requiring affective and cognitive empathy (Mutschler et al., 2013; Sebastian et al., 2012). Taken together, CD has been linked to neural abnormalities in function and structure underlying mechanisms linked to eye gaze and empathy abilities.

### 1.3.2 Facial emotion processing deficits in autism spectrum disorders

ASD is a neurodevelopmental disorder displayed by restricted interests and deficits in social interaction and communication (American Psychiatric Association, 2013). Individuals with ASD often exhibit difficulties in facial emotion recognition, emotion regulation and empathic abilities (Harmsen, 2019; Reyes et al., 2019; Yeung, 2022). Interestingly, atypical facial emotion processing displayed by atypical eye gaze, together with differences in social attention, have been described

as strong early predictors for ASD (Itier & Batty, 2009; Klin et al., 2020; Schultz, 2005; Tiede & Walton, 2021).

#### *1.3.2.1 Impact of eye gaze*

First suggestions link atypical eye gaze in ASD to differences in the "self" concept compared to non-autistic populations (van der Zee & Derksen, 2020). Described as a syndrome of complete self-focus, individuals with ASD differ in their attentional focus and, thus, pay less attention to other people's facial cues than non-autistic people. This shift in attentional focus then leads to salient facial and social cues being missed, which might be an explanation as to why reduced affective and social responsiveness is a diagnostic criterion for ASD (American Psychiatric Association, 2013). Additionally, reduced eye gaze has been linked to deficits in emotion recognition (Bal et al., 2010) and social functioning in ASD (Riddiford et al., 2022). It has been suggested that individuals with ASD show differences in perceiving the face as a whole, which is reflected by reduced fixation and processing of holistic information through the eye region (Harms et al., 2010; Tanaka & Simonyi, 2016; Yanbin et al., 2018) and, instead, fixating on facial details (e.g. mouth) (Joseph & Tanaka, 2003).

#### *1.3.2.2 Impact of callous unemotional traits*

More than 50% of ASD patients exhibit high levels of CU traits (Leno et al., 2015). Thus, autistic traits and CU traits can often co-occur (Carter Leno et al., 2021; Pasalich et al., 2014). This suggests a potential symptomatic overlap between ASD and youth with high CU traits, as has been described in previous studies (Carter Leno et al., 2015, 2021; Frick et al., 2013; Herpers et al., 2016; Ibrahim et al., 2019; Kaat & Lecavalier, 2013; Pijper et al., 2016). Commonly described as a "double hit", individuals with ASD and high CU traits are characterized by severe antisocial behavior and deficits in the ability to recognize negative facial expressions (J. Rogers et al., 2006). First indications also show an interaction effect with co-occurring ASD and CU traits displaying lower levels in empathy than those with only CU traits (Pasalich et al., 2014). Given that ASD has been mainly linked with cognitive empathy deficits (Gillespie-Lynch et al., 2017; Lombardo et al., 2016; K. Rogers et al., 2007; Schwenck et al., 2012; Shalev et al., 2022; Smith, 2006, 2009) and, CU traits being linked to affective and cognitive empathy deficits (Waller et al., 2020), it is conceivable that combining the emotion processing deficits associated with ASD and CU traits would result in more severe and extensive impairments. So far, studies have not investigated the potential influence of CU traits on emotion processing deficits in ASD in comparison to other disorders with CU traits. The neural underpinnings of eye gaze, facial emotion processing and empathy deficits might

however, shed some light on underlying mechanisms that are shared by other conditions and those specific to ASD.

#### *1.3.2.3 Neural findings*

In ASD, neuroimaging studies have shown that atypical processing of emotional facial expressions is linked to atypical functioning of the amygdala (Ashwin et al., 2007; Ishitobi et al., 2011; Kleinhans et al., 2011), hypothalamus and basal ganglia (Aoki et al., 2015), and reduced activation in the vmPFC (Ashwin et al., 2007; Leung et al., 2015). Gaze differences to the eyes in facial expressions might, thus, be linked to atypical brain activation patterns and could potentially help to explain the deficits in facial emotion processing often reported in ASD. Brain structural alterations have also been found in the medial prefrontal cortex (mPFC) and the temporoparietal junction (TPJ) (Hoffmann et al., 2016; O'Nions et al., 2014). Apart from being linked to cognitive empathy, these regions are also involved in global empathy processes including both affective and cognitive aspects (Preckel et al., 2018; Walter, 2012) such as the "self-other distinction" aspect of ToM (Preckel et al., 2018; Schulte-Rüther et al., 2007; Vogeley et al., 2001) or affective ToM processing (Kipps & Hodges, 2006; Mitchell & Phillips, 2015; Shamay-Tsoory et al., 2005, 2006; Shamay-Tsoory & Aharon-Peretz, 2007). Thus, the neural underpinnings of differences in eye gaze and empathy abilities might indicate a potential overlap in emotion processing deficits in ASD and CD. This raises the question of potentially shared or transdiagnostic influences on emotion processing deficits in both disorders.

### 1.3.3 Potential transdiagnostic factors of atypical emotion processing

In transdiagnostic approaches, potentially shared mechanisms are investigated by focusing on overlapping features of different types of deficits or comorbidities and, thus, view mental health problems as a dimension or across a continuum (Haslam et al., 2012; Kotov et al., 2017; Waszczuk et al., 2017). Relatedly, atypical gaze patterns to facial emotion stimuli and impairments in associated processes, such as empathy, are frequently reported in youth with ASD and youth with CD and high CU traits, (R. J. R. Blair, 2005; Carter Leno et al., 2023; Frick et al., 2005; Jones et al., 2010; Menks et al., 2021).

A direct comparison of ASD and CD with high CU traits revealed reduced fixation to the eyes in both disorders (Bours et al., 2018), which implies a potential overlap in eye gaze patterns. However, the eye avoidance hypothesis of autism face processing (Tanaka & Sung, 2016) has gained recent support (Stuart et al., 2022), proposing that atypical gaze behavior is a strategy to avoid unpleasant hyperarousal. By comparison, reduced eye gaze in youth with CD and high CU

traits has been linked to a hypo arousal or lack of interest (Dadds et al., 2006; Demetriou & Fanti, 2022; Waller et al., 2015). Thus, while atypical gaze might be transdiagnostic, the underlying mechanisms might be disorder specific. So far, only two studies have investigated the link between reduced eye gaze and underlying brain functioning of facial emotion processing deficits in ASD and CD. Findings suggest that a hypoactivity in the insula activation in youth with CD and atypical amygdala activation in youth with ASD might be linked to eye gaze behavior (Menks et al., 2021; Stuart et al., 2022). Moreover, eye gaze behavior has been found to partly explain insula hypoactivity in CD (Menks et al., 2021).

CU traits are broadly described by prosocial behavior deficits or antisocial behavior. Emotion processing has been suggested to play a crucial role in the development of antisocial behaviors (Van Goozen et al., 2007), which notably covers a range of different clinical diagnoses and behaviors (Skeem et al., 2014; Stadler, 2010). Thus, although the CU traits phenotype is presented as a specific subgroup of CD, closer inspections lead to questioning whether CU traits are so specific to one diagnosis after all. Apart from CU traits being linked with CD (American Psychiatric Association, 2013), CU traits are found in many disorders with emotion processing deficits (Herpers et al., 2012). Given that CU traits can be present in youth with CD and youth with ASD (Carter Leno et al., 2015, 2021; Kahn et al., 2012), and are linked to global empathy deficits (Waller et al., 2020) they might also represent a transdiagnostic indicator for the empathy deficits displayed by both disorders. Thus, CU traits might play an important role in the understanding and treatment of empathy deficits in CD and ASD.

Taken together, youth with CD and youth with ASD have shown reduced fixation to the eyes in facial expressions, CU traits prevalence rates and reduced empathic affect. This implies a possible overlap in ASD and CD with CU traits and potentially shared impairments which might partially be explained by atypical gaze patterns or the presence of co-occurring CU traits. Investigating potential transdiagnostic factors between disorders based on their shared impairments and underlying neural mechanisms might, thus, also help advance disorder specific knowledge. However, studies have not yet investigated a potential transdiagnostic influence of gaze behavior and CU traits in CD in comparison with ASD.

### 1.4 Emotion regulation in conduct disorder

Emotion regulation is described as a goal-directed process to influence the intensity, duration, and type of experienced emotion (J. J. Gross, 1998; McRae & Gross, 2020). It has gained wide recognition as a transdiagnostic factor for many psychological disorders (Kring & Sloan, 2009; Krueger & Eaton, 2015; Sloan et al., 2017) and has been associated specifically with aggressive

and antisocial behavior (J. T. Gross & Cassidy, 2019; Gülay Ogelman & Fetihi, 2021). Interestingly, low heart rate variability (HRV) has also been associated with antisocial and aggressive behaviors (Portnoy & Farrington, 2015) and is described as an index for emotion regulation deficits (Appelhans & Luecken, 2006).

### 1.4.1 Heart rate variability and emotion regulation

Low HRV has been hypothesized as a potential biomarker for CD symptomatology (Fairchild et al., 2019). Given however, that CD symptomatology is heterogeneous, first indications suggest that HRV levels are on opposite sides of the spectrum, depending on the clinical phenotype (Fanti, 2018). Accordingly, those with high CU traits show high, while those with comorbid internalizing problems show low HRV indices (Fanti, 2018; Fanti et al., 2019). How these differences in HRV might be linked to the emotion regulation deficits often described in CD is, however, not yet fully understood.

#### *1.4.1.1 Heart rate variability as a marker for generic self-regulation*

Apart from being described as an index of emotion regulation, HRV has also been recognized as a transdiagnostic biomarker for self-regulation abilities and psychopathology (Beauchaine & Thayer, 2015; Holzman & Bridgett, 2017; Zahn et al., 2016). Self-regulation is defined as a goal-directed behavior requiring cognitive and emotional regulation or inhibition of contradicting behavior for that goal (Robson et al., 2020). Self-regulation abilities in childhood can predict mental health outcomes later in life (C. Blair & Raver, 2015; Heatherton & Wagner, 2011; Pandey et al., 2018; Robson et al., 2020). These can include unemployment, aggressive and criminal behavior, depression, anxiety, obesity, cigarette smoking, alcohol and substance abuse, and symptoms of physical illness in adulthood (Robson et al., 2020).

#### *1.4.1.2 Neural findings*

Since HRV is part of the autonomic nervous system (ANS), it is linked to brain structures of the Central Autonomic Network (CAN) (Thayer et al., 2009; Thayer & Lane, 2007) which overlap with neural abnormalities linked to emotion regulation and generic self-regulation (Beauchaine & Thayer, 2015; Thayer et al., 2009, 2009; Thayer & Lane, 2007; Thayer & Siegle, 2002; Thayer & Sternberg, 2006). More specifically, HRV mirrors parasympathetic nervous system activity which has consistently been linked to self-regulation processes (Thayer et al., 2009; Thayer & Lane, 2007). Abnormalities in brain structures linked to HRV and self-regulation abilities, have also been associated with CD (Fairchild et al., 2019; Noordermeer et al., 2016; Raschle et al., 2015; J. C.

Rogers & De Brito, 2016). Thus, at the neural level, there might be a potential link between HRV and self-regulation abilities in CD.

Given that HRV has been understood as an index for generic self-regulation skills, the differences in HRV within CD, therefore, might be linked to generic self-regulation rather than emotion regulation abilities.

### 1.5 Research gap

Although emotion processing impairments are described as a core feature in CD and ASD, individuals still differ from each other based on their clinical representations (American Psychiatric Association, 2013). This not only challenges investigations to identify disorder specificities in emotion processing deficits but also current diagnostic criteria which is based on classifications limiting treatment options for the diverse needs of these individuals. Until recently, research has mainly relied on behavioral symptoms in terms of personality and psychopathology manifestations but is starting to integrate other domains such as neural and psychophysiological underpinnings. Moreover, by directly comparing disorders based on overlapping emotion processing impairments in different domains potential transdiagnostic factors might then explain the shared deficits described in CD and ASD. In turn, this might enable the identification of disorder specific emotion processing deficits. Therefore, the first aim was to investigate whether reduced eye gaze represents a potentially transdiagnostic factor for facial emotion processing deficits at the behavioral and neural level. The second aim was to explore whether co-occurring CU traits represent a potentially transdiagnostic factor for reported empathy deficits and underlying brain structures. Since eye gaze and empathy have been directly linked with each other, a potential association between empathy and eye gaze is investigated to determine if the link is also transdiagnostic or not. Moreover, high CU traits have been linked with empathy deficits and eye gaze in youth with CD (Bedford et al., 2015, 2017; Billeci et al., 2019; Ciucci et al., 2015; Dadds et al., 2006, 2008; Demetriou & Fanti, 2022; Frick & Morris, 2004; Huffman & Oshri, 2022; Levantini et al., 2022; Martin-Key et al., 2017; White et al., 2016; Woodworth & Waschbusch, 2008). Given however, the symptomatic overlap of CU traits and ASD (American Psychiatric Association, 2013) it is unclear if CU traits impact the association between empathy and eye gaze in a transdiagnostic or disorder specific way or if the association goes beyond the influence of co-occurring CU traits. Thus, the impact of CU traits on the association between empathy abilities and eye gaze was explored. Lastly, the third aim was to examine whether differences in HRV are more linked to generic self-regulation rather than to emotion regulation abilities and neural structures.

### 1.6 Aim of the study

The studies conducted in this project test the following hypotheses:

1) **Reduced attention to the eyes is a transdiagnostic factor for facial emotion processing deficits in youth with ASD and youth with CD:**

   a) Youth with ASD and youth with CD show less fixations to the eyes during facial emotion processing compared with the TD group (ASD, CD < TD).

   b) Youth with ASD and youth with CD show lower brain activation during facial emotion processing compared with the TD group (ASD, CD < TD).

   c) Differences in brain activation during facial emotion processing are reduced when controlling for gaze behavior.

2) **CU traits are a transdiagnostic factor for empathy deficits in youth with ASD and youth with CD:**

   a) Youth with ASD and youth with CD report lower empathy abilities compared with typically developing peers.

   b) High CU traits are negatively linked to reported empathy deficits in youth with ASD and youth with CD compared with typically developing peers.

   c) High CU traits are negatively linked to differences in brain structures associated with empathy processes in youth with ASD and youth with CD compared with typically developing peers.

**2.1) Additional Hypothesis: Linking empathy abilities to eye gaze behavior**

   a) Eye gaze ability is positively linked to empathy abilities across all participants.

   b) High CU traits influence the link between eye gaze and empathy abilities.

3) **HRV as an indicator for self- regulation abilities in youth with and without CD:**

   a) HRV is positively linked to self- regulation abilities during an emotional go/no-go paradigm across all participants.

b) HRV is associated with brain structures linked to self- regulation processes across all participants.

## *2. Study 1: Gaze behavior, facial emotion processing and neural underpinnings: A comparison of adolescents with autism spectrum disorder and conduct disorder*

Antonia Tkalcec[1], Alessandro Baldassarri[1], Alex Junghans[1], Vithusan Somasundaram[1], Willeke M. Menks[2,3], Lynn V. Fehlbaum[4], Réka Borbàs[4], Nora Raschle[4], Gudrun Seeger-Schneider[5], Bettina Jenny[5], Susanne Walitza[5], David M. Cole[6], Philipp Sterzer[6], Francesco Santini[7], Evelyn Herbrecht[1], Ana Cubillo[1]* & Christina Stadler[1]*

1- Child and Youth Psychiatry, University Psychiatric Clinic, Basel, Switzerland
2- Donders Institute for Brain, Cognition and Behaviour, Radboud University, and Radboud University Medical Centre, Nijmegen, the Netherlands
3- Max Planck Institute for Psycholinguistics, Nijmegen, the Netherlands
4- Jacobs Center for Productive Youth Development, University of Zurich, Zurich, Switzerland
5- Child and Youth Psychiatry, Psychiatric University Clinic, University of Zurich, Zurich, Switzerland
6- Translational Psychiatry, University Psychiatric Clinic, Basel, Switzerland
7- Radiological Physics Department, University Hospital, Basel, Switzerland

* AC and CS should be considered joint senior author

**Abstract**

**Background**. Facial emotion processing deficits and atypical eye gaze are often described in individuals with autism spectrum disorder (ASD) and those with conduct disorder (CD) and high callous unemotional (CU) traits. Yet, the underlying neural mechanisms of these deficits are still unclear. The aim of this study was to investigate if eye gaze can partially account for the differences in brain activation in youth with ASD, with CD and CU traits and typically developing youth (TD).
**Methods**. 105 adolescent participants ($N_{CD}$ = 39, $N_{ASD}$ = 27, $N_{TD}$ =39; mean age = 15.59 years) underwent a brain functional imaging session including eye tracking during an implicit emotion processing task while parents/caregivers completed questionnaires. Group differences in gaze behavior (parameters: number of fixations to the eye and mouth regions) were investigated using Bayesian analyses. Full-factorial models were used to investigate group differences in brain activation with and without including gaze behavior parameters and focusing on brain regions underlying facial emotion processing (insula, amygdala and medial prefrontal cortex). **Results**. Youth with ASD showed increased fixations on the mouth compared to TD and CD groups. In the CD group, high CU traits were associated with less fixations to the eye region compared to TD for all emotions. Brain imaging results show higher left anterior insula activation in the ASD compared with the CD group when angry faces were presented. The inclusion of gaze behaviour parameters in the model only reduced the size of that cluster.
**Conclusion**. Differences in insula activation may be partially explained by gaze behavior. Thus, targeting gaze behavior in interventions might be potentially beneficial for disorders showing impairments associated with processing of emotional faces.

## 1. Introduction

Facial emotion processing is a fundamental skill for prosocial behavior. From the early years of life, babies usually display a natural preference to look at faces (Goren et al., 1975; Valenza et al., 2019). The eye region is described as a main source for social information, nonverbal social interaction, and learning (Adams & Nelson, 2016; Batki et al., 2000; Hamilton, 2016; Mundy & Newell, 2007). Thus, attention to the eyes is crucial for the accurate processing of facial expressions (Schindler & Bublatzky, 2020). Deficits in processing facial expressions are linked to problems in social situations which are main difficulties exhibited by individuals with autism spectrum disorders (ASD) and antisocial behaviors among others (Dawel et al., 2012; Dolan & Fullam, 2006; Fairchild et al., 2009, 2010; Marsh & Blair, 2008).

ASD is defined by restricted interests, deficits in social interaction and social communication and reduced empathic responsiveness (American Psychiatric Association, 2013). Although ASD is a heterogeneous disorder linked to varying genetic and neurobiological factors (Constantino et al., 2021; C. N. Johnson et al., 2021; Klin et al., 2020) reduced eye contact is one of the most early signs for ASD (Constantino et al., 2021; Klin et al., 2020) linked to deficits in emotion processing and social functioning (Riddiford et al., 2022). Reduced fixation to the eyes has also been reported in children and adolescents with conduct disorder (CD) and high callous unemotional (CU) traits (Billeci et al., 2019; Dadds et al., 2006, 2008, 2014; Demetriou & Fanti, 2022) and hypothesized to potentially underlie the facial processing deficits described in those with high CU traits (Dadds et al., 2008, 2014). The CD phenotype with high CU traits is characterized by more persistent and severe patterns of antisocial, aggressive, and delinquent behaviors (Frick & White, 2008). CU traits are defined by a lack of remorse, empathy, and shallow affect (Frick, 2017a) in addition to profound impairment in emotion processing (Billeci et al., 2019; Hartmann & Schwenck, 2020; Moore et al., 2019). This is especially the case when negative emotions were presented (Billeci et al., 2019; Ciucci et al., 2015; Martin-Key et al., 2017; White et al., 2016). Furthermore, the link between CU traits and reduced eye gaze might even be detectable from early childhood (Bedford et al., 2015, 2017).

Although it is well established that these facial emotion processes involve interactive brain networks (Vuilleumier & Pourtois, 2007), the disorder specific neural underpinnings are still unclear. In ASD, different theories suggest that reduced eye gaze is based on opposite neural functioning responses in the amygdala. On the one hand, the amygdala theory of autism suggests lack of eye contact is caused by a hypoactivity in the amygdala (Baron-Cohen et al., 2000). On the other hand, the eye avoidance hypothesis proposes that eye gaze is based on amygdala hyperactivity

(Tanaka & Sung, 2016). Accordingly, it has been shown that ASD patients exhibit higher unpleasant arousal in response to eye contact than neurotypicals, mirrored by amygdala hyperactivity (Tanaka & Sung, 2016). As a strategy to reduce this unpleasant hyperarousal, direct eye contact is avoided which would be consistent with reports from individuals on the autism spectrum stating that direct eye gaze induces stress and anxiety (Trevisan et al., 2017) and a recent meta-analysis suggesting that atypical amygdala activation is linked to eye avoidance (Stuart et al., 2022). Taken together, in youths with ASD, atypical eye gaze behavior might be linked to altered brain functioning especially in the amygdala.

Atypical activity in the amygdala, as well as in the insula and orbitofrontal cortex (OFC) during facial emotion processing were repeatedly found in youth with CD and high CU traits (Berluti et al., 2023; Jones et al., 2009; Viding et al., 2012). More specifically, CU traits have been linked to a hypoactivity in the amygdala in response to fearful facial expressions (Lozier et al., 2014) supporting theories that those with high CU traits display reduced empathic responses to emotional distress cues (Dadds et al., 2014). This also highlights the relevance of CU traits as an important phenotype for empathic responses and atypical brain activation patterns in CD. As in youth with ASD, amygdala dysfunction in youth with CD has been linked to atypical gaze behavior and facial emotion processing deficits indicating potentially interrelated underlying neural mechanisms in these disorders. Yet, possible disorder-specificities in these associations are still unknown.

Neuroimaging comparison studies directly comparing youth with ASD and CD are scarce. However, first indications showed that fixations to the eyes was reduced in youth with ASD and CD compared to a healthy control group indicating a potential overlap in differential gaze behavior (Bours et al., 2018). Few studies have focused on differences in brain function during empathy processes showing reduced activation in the amygdala during affective empathy in both disorders but also differential brain activation patterns (Klapwijk et al., 2016; O'Nions et al., 2014; Vilas et al., 2021). Compared with healthy controls, youth with ASD show reduced vmPFC responses during different cognitive empathy processes in ASD youth and lower brain responses during affective empathy processes in anterior insula and left inferior gyrus in CD (Klapwijk et al., 2016; O'Nions et al., 2014). However, the underlying disorder specific neural mechanisms of facial emotion processing deficits exhibited by ASD and CD are still unclear. A previous study showed that neural group differences in the insula during emotion processing between adolescents with ASD and typically developing youth (TD) are reduced when controlling for eye gaze behavior

indicating that emotion processing deficits may be partly explained by gaze behavior differences (Menks et al., 2021). Studies have, however, not yet investigated this in youth with ASD.

In sum, impairments in facial emotion processing and a lack of attention to the eyes are detectable from early childhood and are characteristic for youth with ASD and youth with CD and high CU traits. However, whether these impairments are underpinned by similar neural mechanisms still requires further clarification. It is also of major interest to further investigate whether neural abnormalities in facial emotion processing in CD and ASD are linked to differences in eye gaze behavior. Functional imaging results (Ashwin et al., 2007; Cohn et al., 2013; Dadds et al., 2014; Fairchild et al., 2014; Leung et al., 2015; Menks et al., 2021; Passamonti et al., 2010; Stuart et al., 2022) suggest a partial overlap in how eye gaze might be linked to brain activation differences during facial emotion processing. Considering the link between fixation to the eyes and brain function, atypical brain activity patterns might be associated with atypical gaze behavior in ASD and CD.

Based on previous findings (Ashwin et al., 2007; Cohn et al., 2013; Dadds et al., 2014; Fairchild et al., 2014; Leung et al., 2015; Menks et al., 2021; Passamonti et al., 2010; Stuart et al., 2022), we hypothesize more fixations to the eyes in TD than youth with ASD/CD independently of the emotion presented. Furthermore, we expect the levels of CU traits to be inversely correlated with the number of fixations to the eye region in the CD group. At the neural level, we expect that youth with ASD/CD would show reduced vmPFC activation compared to TD (TD > CD, ASD) and that youth with CD would show reduced insula and amygdala activation compared to TD and youth with ASD during facial emotion processing (CD < TD, ASD). Finally, we hypothesize the relationship between facial emotion processing and neural activation in insula, amygdala and vmPFC to be influenced by the number of fixations to the eye/mouth region. We, thus, expected neural differences to be partly reduced when controlling for the number of fixations.

## 2. Methods

### 2.1 Participants

Adolescent participants with ASD and CD were recruited from different specialized clinical settings and residential centres in Basel and Zurich while TD participants were recruited from socioeconomically diverse secondary schools in Canton Basel-Stadt. Participants in the ASD and CD group needed to fulfil the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013) for either diagnoses, with no comorbid depressive or anxiety disorder. The requirement for inclusion in the TD group was no current or previous diagnosis of any psychiatric disorder. A semi-structured clinical interview

(Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version, K-SADS-PL) (Kaufman et al., 1997a) was conducted to evaluate diagnostic inclusion criteria. For the ASD group, the Autism Diagnostic Observation Schedule (ADOS) or Autism Diagnostic Interview - revised (ADI-R) (Bölte et al., 2006; Poustka et al., 2015) was additionally administered. Furthermore, only participants with an average IQ score (>70) were included in the study. Due to the IQ criteria, the ASD group consequently consisted of youth who fulfilled diagnostic criteria for either Asperger's syndrome or high functioning autism. Participants underwent a functional brain imaging data acquisition session and caregivers filled out reports on attention problems (subscale of the Childhood Behavior Check List) (Achenbach et al., 2001) and CU traits (Inventory of Callous Unemotional traits, ICU) (Frick, 2017a). Written informed assent and/or consent was obtained from participants and caregivers. All procedures were conducted in accordance with the Declaration of Helsinki and approved by the local Ethics Committee (EKNZ, 2019-02386).

The initial sample consisted of 125 adolescent participants of which 20 were excluded from analysis due to poor gaze data quality. Thus, the final sample included in the gaze behavior analysis consisted of 105 adolescents ($N_{CD}$ = 39, $N_{ASD}$ = 27 and $N_{TD}$ =39) aged 10 to 18 years ($M$=15.59; $SD$=1.97 years). For the functional Magnetic Resonance Imaging (fMRI) analysis, data from 3 additional participants had to be excluded due to incomplete data ($N_{CD}$=2, $N_{TD}$=1). Thus, the final imaging sample consisted of 102 participants ($N_{CD}$=37; $N_{ASD}$=27; $N_{TD}$=38). The data were collected in two waves from 2015 to 2023 with a time lag of 18 months between waves. Data of 57 participants were collected in the first ($N_{CD}$=21; $N_{ASD}$=2; $N_{TD}$=34) and 48 in the second wave. Additionally, for the presentation of the implicit facial emotion processing task, different programs were used: Presentation® software (Neurobehavioral System, Inc.) in the first, and E-Prime® in the second data collection wave. To account for potential differences during data collection, we included data collection wave as an additional regressor of no interest in all analyses to account for potential differences during data collection. Further details on the sample characteristics are shown in table 1.

### 2.2 fMRI implicit facial processing task

An adapted version of the implicit emotional face processing paradigm from Passamonti and colleagues (2010) was used after successful application in previous studies (Fairchild et al., 2010; Menks et al., 2021; Passamonti et al., 2010). Photographs from 30 different individuals from the NimStim Face Stimuli Set (Tottenham et al., 2009) consisting of neutral, angry, and fearful facial

expressions were presented on a grey background without non-facial features (hair, ears). Participants were instructed to indicate the gender of each face and to fixate on the white crosses shown in between stimuli (figure 1).

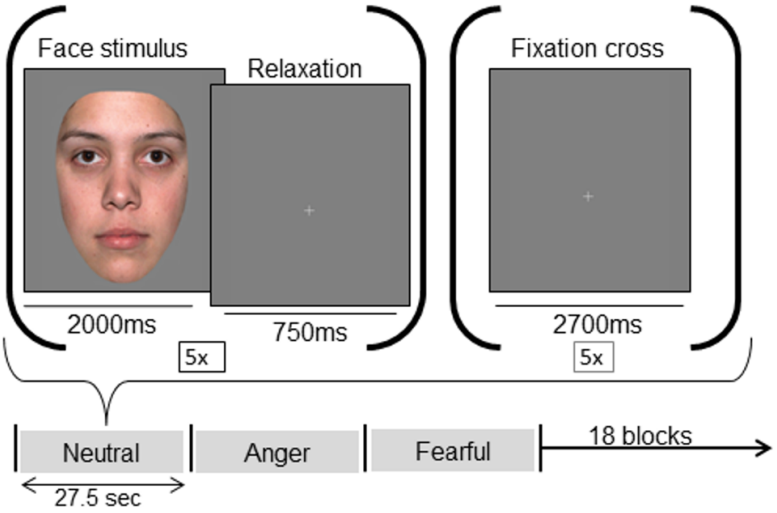


*Figure* 1. This figure shows the implicit Facial Emotion Processing Task used for the eye tracking and fMRI analysis (see ((Menks et al., 2021))). *Face stimulus = presentation of a facial stimuli, fixation cross = presentation of a fixation cross*

The task was presented in a block design, with five different facial stimuli trials of the same emotional expression (neutral, anger, or fearful) intermixed with five fixation trials and pseudo-randomized by gender and trial type (face/fixation) per block. In face trials, a face stimulus was presented for 2 seconds followed by a fixation cross for 750 milliseconds. In fixation trials, the fixation cross on the grey background was presented for 2700 milliseconds. The task was conducted in two runs, each consisting of twelve blocks per emotion (60 neutral, 60 anger, 60 fearful). For each facial stimulus, eye gaze behavior (number of fixations and fixation duration) and task performance were recorded (for more information on task characteristics see (Menks et al., 2021)). Descriptive analysis results per group for task performance can be found in table 1.

### 2.3 Eye tracking data acquisition

The eye-tracking device model of VisualSystem USB 60x3 produced by Nordic NeuroLab, Bergen, Norway was used with the ViewPoint software by Arrington Research®. Eye movements were recorded at a rate of 60 Hz. The device was attached to the right ocular of the binocular video goggles. The raw data provided by the interface was in the form of pairs of coordinates identifying the pupil location in the field of view of the camera. Monitor distance was 10 cm with a size of

14.3 by 10.7 cm and a resolution of 800 x 600 pixels. To ensure an equal eye-tracking starting position for each trial, a fixation cross was located on the nose bridge in between the eyes and mouth location of the stimuli during the fixation trials. Prior to recording, the camera was adjusted to ensure clear vision for the participant and was centrally located at the participants right eye for satisfactory data recording. At the beginning of each run, a 9-point calibration was performed. Calibration was repeated until satisfactory.

### 2.4 Functional imaging data acquisition

Whole brain functional magnetic resonance images were obtained using a 3T MR imaging system (Siemens Prisma) and a 20-channel phased-array radio frequency head coil. After automatic second- order shimming of the magnetic field, functional whole-brain volumes were acquired using a T2*weighted echo-planar imaging (EPI) sequence: TR=2500ms; TE=30ms; flip angle=83°; FoV= 192mm; 41 slices; matrix size=64x64; and voxel size=3x3x2mm$^3$. To allow a steady magnetization before the task started, the first four functional time points of each run were discarded. Additionally, a high-resolution T1-weighted Magnetization-Prepared Rapid Acquisition Gradient Echo (M-PRAGE) dataset was acquired with the following parameters: TR=1900.0ms; TE=3.42ms; flip angle=9°; FoV=256mm; matrix size=256x256; and voxel size=1x1x1mm$^3$.

### 2.5 Gaze behavior analysis

The raw data were processed in Matlab as well as the EyeMMV toolbox (Krassanakis et al., 2014) and analyzed using R (Version 4.2.1, RStudio Version 2022.7.0.547) (R Core Team, 2020; RStudio Team, 2022). Two areas of interest (AOI) were defined. One AOI concentrated on the eyes of each facial stimulus and the other AOI concentrated on the mouth. Both AOIs were rectangular and the same size. Positions of the AOIs on the screen were the same across all stimuli. The main measures of gaze behavior are number of fixations on the eye region and on the mouth region per emotion and across all emotions. Fixations were defined using the fixation identification algorithm implemented in the EyeMMV (Krassanakis et al., 2014) as having a minimum duration of 150 milliseconds and using the parameters t1 = 0.05, t2 = 0.1, minDur = 150, maxx = 1, maxy = 1. Blinks and offscreen events were removed before calculating fixations and gaze data during each trial was corrected for head movements. To ensure data quality, participants with poor gaze data were removed from analysis. Participants were excluded if more than 60% of their trials had <500ms of usable gaze data, the calibration failed, or if the eye tracking system malfunctioned. Number of fixations were calculated by dividing the fixation count for each AOI by the total

fixation count for the entire screen. The dependent variables were calculated for each trial and then averaged for each emotion (neutral, angry, or fearful). Likewise, fixation duration was also calculated by dividing the duration of fixations within each AOI by the total duration of fixations on the entire screen.

From the whole dataset, missing data represent 6.67 % of the ICU and 26.67 % of the CBCL. Using the "mice" package, multiple imputation by chained equations were implemented (van Buuren & Groothuis-Oudshoorn, 2011) (m = 100, maxit = 20, meth = "pmm") to maximize the data used for those analyses. We investigated group differences in eye gaze behavior (number of eye/mouth fixations) using 2 models within a Bayesian multilevel framework, with the group values entered as the main regressor of interest and gaze behavior (number of fixations to the eyes/mouth) as the dependent variable for the emotions: angry, fearful and neutral. The models included age, sex, IQ, the CBCL attention problem subscale scores and data collection wave as regressors of interest. Additionally, the total sum scores of the ICU were added to investigate the hypothesized interaction effect of the CD group and co-occurring CU traits on gaze behavior. Models included a flat prior and a Gaussian likelihood distribution, with parameters warmup = 2000, iter = 4000, 4 chains, and 3 cores. All variables were standardized before being entered in the analyses. Additionally, supplementary analysis was conducted for fixation durations on the eye and mouth regions as dependent variables.

**2.6 fMRI analysis**

Functional neuroimaging data were preprocessed and analyzed in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/), implemented in MATLAB (version 2014b; MathWorks). Preprocessing included data quality check, slice time correction, realignment, co-registration to the structural images, segmentation of the structural image, normalization to MNI space and smoothing (8mm FWHM). Based on previous studies (Menks et al., 2021; Passamonti et al., 2010), all analyses were restricted to one mask of binarized and 50%-thresholded regions that was built from six regions of interest (ROI) which included bilateral insula, bilateral amygdala and vmPFC of the Harvard Oxford Atlas in FSLeyes (Version 1.3.0) (supplementary figure 1). For each participant, blood-oxygen-level-dependent (BOLD) responses were modeled including six motion regressors to account for motion effects and temporal inhomogeneities and a global regressor for each run to account for differences between runs. Our first level model included emotional face (neutral, anger, fearful) and three fixation conditions (neutral fixation, anger fixation, fearful fixation) as regressors of interest. The following contrasts were created: neutral stimuli>neutral fixation, anger stimuli

>anger fixation, and fearful stimuli >fearful fixation (Fairchild et al., 2014). For the full factorial model, group was set as regressor of interest. Age, IQ, sex, the CBCL attention problems score, the total sum score of the ICU and data collection wave were added as regressors of no interest. Then, to investigate a possible effect of gaze behavior on brain activation differences, the number of fixations to the mouth/eye region per group was included as an additional regressor of interest for each emotion (neutral, anger, fearful). Significant parameters are extracted via FSL, using a mask including the significant cluster region and the respective significant cluster of the FEAT fMRI analysis in FSL (Brett et al., 2002). All results are reported using a cluster-building threshold of p<.001 and a cluster-level correction for multiple comparison of $p < .05$, familywise error (FWE-) corrected.

## 3. Results

### 3.1 Sample characteristics

Group comparisons revealed differences on sex, IQ, CBCL attentive problems (AP) scores and ICU sum scores (table 1). The results also show significant group differences in task performance accuracy for all emotions (table 1). The number of fixations to the eyes and mouth regions per group are depicted in figure 2.

*Table 1.* Sample Characteristics

| | **ASD (N=27)** | | **CD (N=39)** | | **TD (N=39)** | | *Chi square/F Stat* | *p value* |
|---|---|---|---|---|---|---|---|---|
| | *Mean (SD)/ Count (%)* | *NR missing values* | *Mean (SD)/ Count (%)* | *NR missing values* | *Mean (SD)/ Count (%)* | *NR missing values* | | |
| Sex | 11F/16M | 0 | 14F/25M | 0 | 28F/11M | 0 | 11.43 | 0.003 |
| Age (Years) | 14.89 (2.64) | 0 | 15.74 (1.73) | 0 | 15.92 (1.56) | 0 | 2.441 | 0.092 |
| IQ | 105.35 (14.95) | 0 | 97.37 (12.19) | 0 | 105.45 (8.23) | 0 | 5.754 | 0.004 |
| CBCL attention problems | 67.15 (3.96) | 5 | 66.67 (10.46) | 14 | 51.49 (3.96) | 9 | 30.66 | < 0.001 |
| ICU total sum | 29.52 (10.62) | 1 | 31.33 (8.77) | 6 | 18.57 (7.67) | 0 | 22.65 | <0.001 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Task performance Accuracy %** | | | | | | | | |
| anger | 0.8 (0.15) | - | 0.78 (0.17) | - | 0.89 (0.09) | - | 6.036 | 0.003 |
| fearful | 0.83 (0.16) | - | 0.8 (0.17) | - | 0.91 (0.07) | - | 6.03 | 0.003 |
| neutral | 0.84 (0.17) | - | 0.85 (0.19) | - | 0.92 (0.1) | - | 3.247 | 0.043 |

This table displays the mean and standard deviation (SD), number count or percentage (%) for each group (ASD, CD, TD) as well as the group differences for the key demographic variables and questionnaire scores included in further analyses of the study. For each group, the number of participants with missing values for the corresponding value per variable is shown. *ASD = youth with autism-spectrum disorder diagnosis, CD = youth with conduct disorder diagnosis, TD = typically developing youth, NR missing values = number count of missing values, IQ = intelligence quotient (total score of WASI, WISC or WAIS), CBCL attention problems = scores of the attention problems subscale from the CBCL, ICU total sum = total sum score of Inventory for Callous Unemotional traits (ICU).*

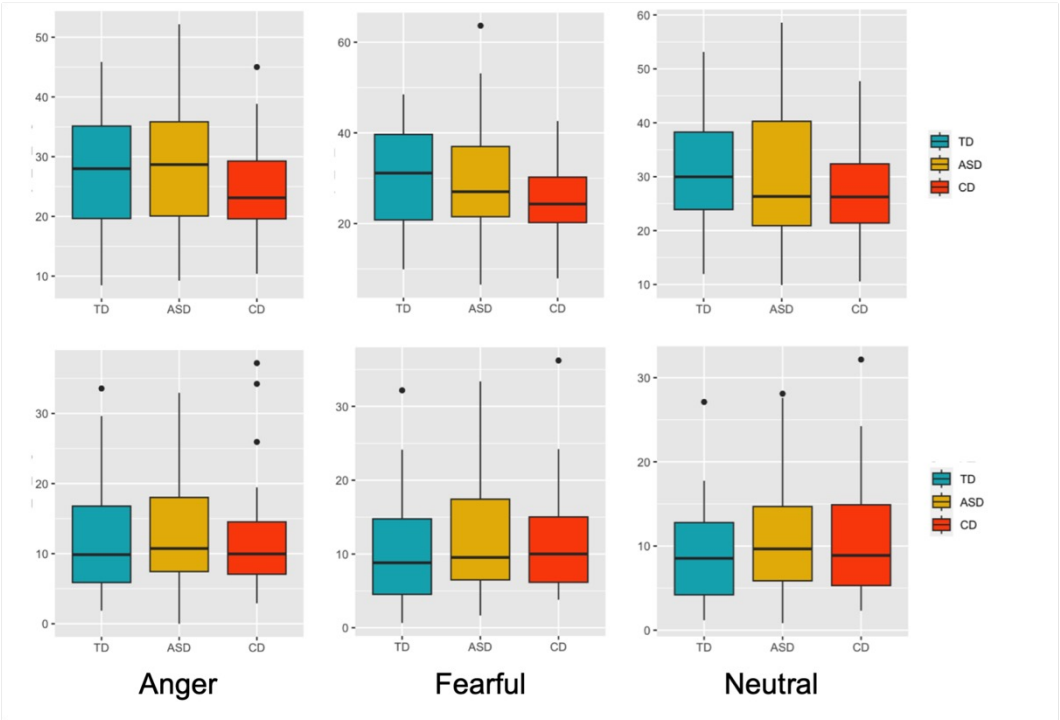

*Figure* 2. Fixations to the eyes (upper row) and mouth regions (lower row) in percentage per group and emotion. *TD = typically developing youth, CD = youth with conduct disorder, ASD = youth with autism spectrum disorder*

### 3.2 Gaze behavior results

Across all emotions, results showed significant group differences. The ASD group displayed a higher number of fixations to the mouth region than the TD and CD groups (table 2). A significant negative interaction effect of the CD group and CU traits for eye gaze across all emotions was shown (table 2, figure 3). For each emotion, the ASD group had significantly more fixations to the mouth for neutral faces than the TD group, for angry faces than the CD group and for fearful faces than TD and CD groups (table 3). Additional supplementary analyses show group comparison results on fixation durations to the eyes and mouth regions (supplementary table 1). Findings revealed that the ASD group showed higher fixation durations to the mouth than TD and CD across all emotions.

*Table 2.* Bayes Multilevel Regression Results

| Fixations to the eyes | | | | | | | |
|---|---|---|---|---|---|---|---|
| | *Estimate* | *Est.Error* | *l-95% CI* | *u-95% CI* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| Angry faces | -0.23 | 0.06 | -0.34 | -0.12 | 1 | 5521 | 5730 |
| Fearful faces | -0.07 | 0.06 | -0.18 | 0.04 | 1 | 5874 | 5591 |
| ASD | -0.29 | 0.42 | -1.11 | 0.53 | 1 | 1200 | 1837 |
| CD | -0.49 | 0.33 | -1.18 | 0.15 | 1 | 1147 | 1969 |
| CU traits | 0.47 | 0.21 | 0.05 | 0.89 | 1 | 1029 | 2234 |
| Male sex | -0.24 | 0.2 | -0.63 | 0.16 | 1 | 1115 | 2356 |
| Age | 0.08 | 0.1 | -0.11 | 0.27 | 1 | 1359 | 2512 |
| IQ | -0.03 | 0.11 | -0.24 | 0.19 | 1.01 | 1046 | 2027 |
| CBCL AP | -0.12 | 0.13 | -0.38 | 0.14 | 1 | 1335 | 2110 |
| Data collection wave | -0.22 | 0.25 | -0.71 | 0.27 | 1 | 1182 | 2415 |
| Interaction ASD x CU traits | -0.49 | 0.29 | -1.06 | 0.09 | 1.01 | 1009 | 2036 |
| Interaction CD x CU traits | -0.66 | 0.3 | -1.26 | -0.07 | 1 | 1080 | 1951 |
| Fixations to the mouth | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% CI* | *u-95% CI* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| Angry faces | 0.27 | 0.05 | 0.17 | 0.37 | 1 | 5582 | 4455 |
| Fearful faces | 0.14 | 0.05 | 0.04 | 0.25 | 1 | 5847 | 4293 |
| ASD | 0.86 | 0.42 | 0.01 | 1.67 | 1 | 1311 | 2308 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| CD | 0.27 | 0.34 | -0.4 | 0.93 | 1 | 1222 | 2197 |
| CU traits | -0.17 | 0.21 | -0.59 | 0.24 | 1 | 1224 | 2306 |
| Male sex | 0.44 | 0.21 | 0.03 | 0.85 | 1 | 1268 | 1943 |
| Age | 0.02 | 0.1 | -0.18 | 0.22 | 1 | 1627 | 2176 |
| IQ | -0.11 | 0.11 | -0.32 | 0.1 | 1 | 1700 | 2446 |
| CBCL AP | -0.09 | 0.13 | -0.35 | 0.18 | 1 | 1788 | 2484 |
| Data collection wave | 0.58 | 0.26 | 0.07 | 1.11 | 1 | 1444 | 1902 |
| Interaction ASD x CU traits | 0.13 | 0.29 | -0.44 | 0.67 | 1 | 1233 | 2379 |
| Interaction CD x CU traits | 0.21 | 0.29 | -0.36 | 0.79 | 1 | 1265 | 2398 |

Bayes multilevel regression analysis results testing the one-sided hypotheses on key dependent variables: Number of fixations to the eyes and mouth regions. *Est. = Estimate or mean, Est. Error = estimation standard deviations, l-95% CI = lower credible interval, u-95% CI = upper credible interval, Rhat = convergence of the MCMC algorithm (Gelman and Rubin, 1992), Bulk_ESS = bulk effective sample size estimate, Tail_ESS = tail effective sample size estimate, ASD = youth with autism spectrum disorder, CD = youth with conduct disorder, TD = typically developing youth, CBCL AP = score of the attention problems scale from the parent reported child behavior checklist*

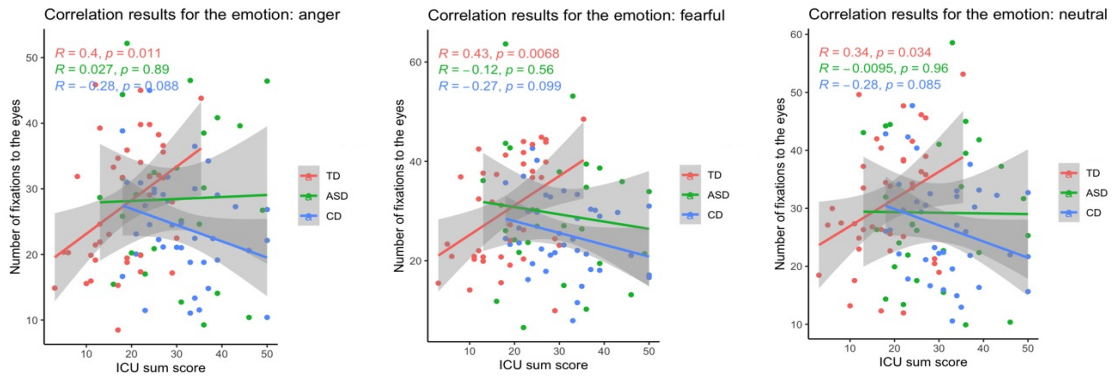


*Figure* 3. Correlation analysis results of ICU sum scores and number of fixations to the eyes for each emotion per group. *TD = typically developing youth, CD = youth with conduct disorder, ASD = youth with autism spectrum disorder*

*Table 3.* Bayes Multilevel Regression Results – Group Comparisons per Emotion

| | Eye Fixations | | | | Mouth Fixations | | | |
|---|---|---|---|---|---|---|---|---|
| | Anger | | | | | | | |
| *Hypothesis* | *Est.* | *SE* | *95% CI* | *Post. Prob.* | *Est.* | *SE* | *95% CI* | *Post. Prob.* |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| ASD<TD | -0.39 | 0.46 | -1.15 | 0.36 | 0.8 | 0.75 | 0.47 | -0.02 | 1.51 | 0.06 |
| CD<TD | -0.53 | 0.37 | -1.14 | 0.06 | 0.93 | 0.15 | 0.36 | -0.44 | 0.76 | 0.34 |
| ASD=CD | 0.14 | 0.32 | -0.38 | 0.65 | 0.32 | 0.6 | 0.32 | 0.07 | 1.12 | 0.03 |
| | | | | | Fearful | | | | | |
| *Hypothesis* | *Est.* | *SE* | *95% CI* | | *Post. Prob.* | *Est.* | *SE* | *95% CI* | | *Post. Prob.* |
| ASD<TD | -0.3 | 0.44 | -1.03 | 0.44 | 0.75 | 1.08 | 0.45 | 0.33 | 1.81 | 0.01 |
| CD<TD | -0.58 | 0.36 | -1.18 | 0 | 0.95 | 0.4 | 0.36 | -0.18 | 1.01 | 0.13 |
| ASD=CD | 0.28 | 0.31 | -0.23 | 0.8 | 0.18 | 0.67 | 0.32 | 0.15 | 1.19 | 0.02 |
| | | | | | Neutral | | | | | |
| *Hypothesis* | *Est.* | *SE* | *95% CI* | | *Post. Prob.* | *Est.* | *SE* | *95% CI* | | *Post. Prob.* |
| ASD<TD | -0.21 | 0.47 | -0.98 | 0.55 | 0.67 | 0.76 | 0.46 | 0.01 | 1.52 | 0.05 |
| CD<TD | -0.38 | 0.37 | -0.99 | 0.22 | 0.85 | 0.25 | 0.37 | -0.36 | 0.85 | 0.24 |
| ASD=CD | 0.18 | 0.32 | -0.35 | 0.71 | 0.28 | 0.5 | 0.32 | -0.02 | 1.02 | 0.05 |

Bayes regression analysis results testing the one-sided hypotheses on key dependent variables: Number of fixations to the eyes and mouth regions per emotion (anger, fearful, neutral). *Est. = Estimate, SE = Standard-Error, 95% CI = Credible interval, Post. Prob = Posterior Probability under the hypothesis against the hypothesis' alternative. Hypothesis = direction of tested hypothesis, ASD = youth with autism spectrum disorder, CD = youth with conduct disorder, TD = typically developing youth*

### 3.3 fMRI results

Initial F tests showed significant group differences for all emotions in numerous regions, most consistently the bilateral anterior insula (supplementary table 2). Insula cluster activation parameters for each emotion and group are displayed in supplementary figure 2. For t test group comparisons, no results survived multiple comparison corrections. Then, post-hoc exploratory analysis revealed increased brain activation in the ASD group compared with the CD group in the left anterior insula specifically when processing angry faces (MNI = 33.4;17.6;4.9, 385 mm3 volume) (figure 4). When the number of eye and mouth fixations were included in the model, the cluster of activation was smaller (MNI = 32.6;18.3;2.7, 157 mm3 volume) (figure 5). Post-hoc Bayesian analysis on the effect of eye gaze on the extracted parameters of the insula cluster showed

a positive main group effect for the ASD group when accounting for differences in fixations to the mouth region (supplementary table 3). For completeness, all analyses were repeated adopting a whole brain approach with no significant results.

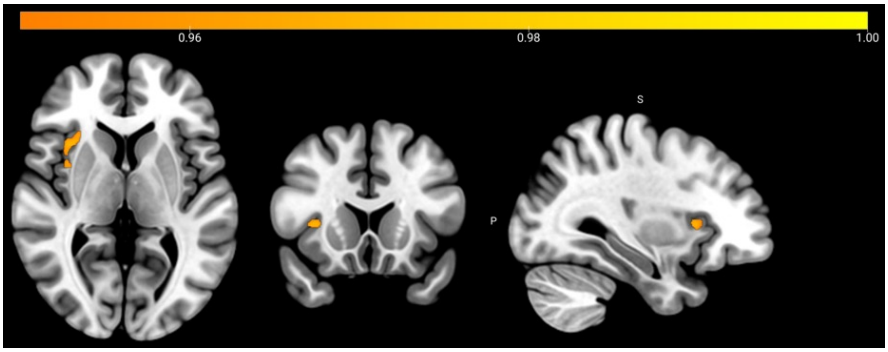


*Figure* 4. Full factorial analyses for the contrast ASD > CD when angry faces are shown. The model included group as regressor of interest and age, sex, IQ, attention problems scores of the CBCL, total sum score of the ICU and data collection wave as regressors of no interest. *CD = youth with conduct disorder, ASD = youth with autism spectrum disorder*

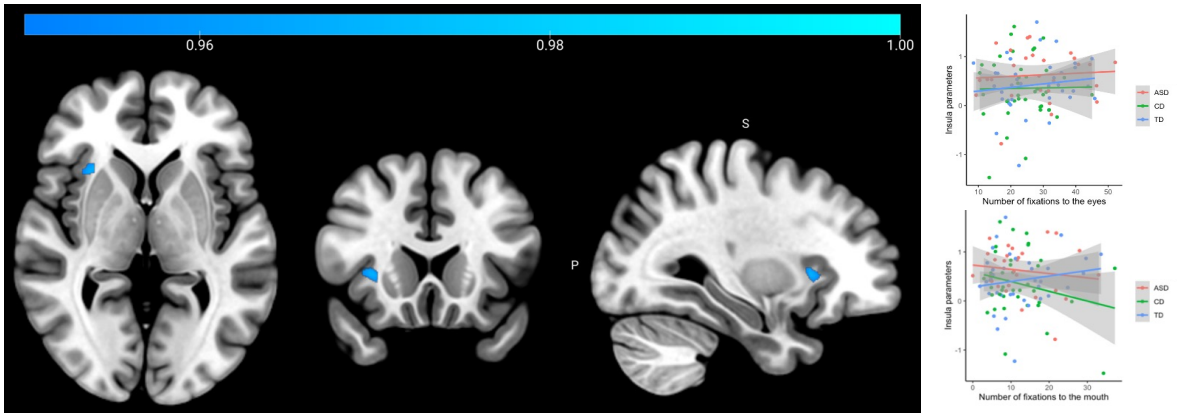


*Figure* 5. Full factorial analyses results including fixations to the eye and mouth region for the contrast ASD > CD when angry faces are shown and correlation results of number of fixations to eyes/mouth and extracted insula parameters for angry faces. *TD = typically developing youth, CD = youth with conduct disorder, ASD = youth with autism spectrum disorder*

## 4. Discussion

The main aim of the study was to investigate the neural correlates of differences in facial emotion processing in ASD and CD and whether these differences can be partially mitigated by differences in gaze behavior. Our results show that the ASD group do not differ from CD or TD youths on eye gaze patterns but show more attention to the mouth region. Additionally, patients with CD showed

reduced attention to the eyes when comorbid CU traits were present. Relative to ASD adolescents, CD youths showed reduced activation in the right anterior insula when angry faces were presented. This cluster was reduced in its size but remained significant when gaze behavior parameters (number of fixations to the eye and mouth) were taken into account.

Compared with the TD group, youths with ASD did not show reduced attention to the eyes but a disorder specific increase in attention to the mouth for fearful and neutral faces. This is in line with studies showing no difference in eye-region fixations between ASD and healthy controls across different contexts (Åsberg Johnels et al., 2014; Kwon et al., 2019). More attention to the mouth in fearful and neutral faces might be linked to deficits in facial processing being described as independent from the emotion, whether it is neutral or negative (Reisinger et al., 2020). These results might also partially align with the mouth/diminished eyes hypothesis of autism which explains this with compensatory strategies used by individuals with ASD that focus more on speech and its social information by fixating more on the mouth than eye region compared to typically developing peers (Klin et al., 2002). Alternatively, there might also be different ways in which a face is processed in individuals with ASD because they focus on facial details of the face instead of salient social information (T. F. Gross, 2005; Joseph & Tanaka, 2003). Compared with the CD group, individuals in the ASD group paid more attention to the mouth when negative emotions (angry, fearful) were presented, suggesting that group differences might be dependent on the emotional valence presented. Our results moreover revealed that youth with CD compared with the TD group show reduced attention to the eyes when high CU traits were present suggesting that atypical eye gaze in CD might be at least partially driven by co-occurring CU traits. This is in line with other studies showing reduced attention to the eyes in youth with high CU traits (Billeci et al., 2019; Hartmann & Schwenck, 2020; Moore et al., 2019). Furthermore, our findings support existing evidence that youth with CD might pay less attention or are less responsive to negative stimuli (Marsh & Blair, 2008; Moore et al., 2019). This would fit with other findings showing reduced responsiveness to punishment in those with high compared to those with low levels of CU traits (R. J. R. Blair, 2017; Hawes et al., 2014; Kochanska, 1993; R. Zhang et al., 2023). In sum, our behavioral findings might indicate that compared with the TD group, youth with ASD and youth with CD and high CU traits showed differences in gaze behavior. The nature of the atypical gaze pattern appears to be disorder-dependent with opposing length of fixation abnormalities for either eye or mouth regions for ASD and CD with high CU traits.

Brain imaging results showed no differences for the ASD or CD group compared with the TD group. This might be potentially related to the large heterogeneity in both disorders, also in

regard to emotion processing deficits (American Psychiatric Association, 2013; Kohls, Baumann, et al., 2020; Sivathasan et al., 2020; Viding & McCrory, 2019). Deficits in gaze behavior have been also mainly investigated in explicit emotion recognition tasks implying that potential facial emotion processing deficits in ASD may be dependent on the task type. However, our findings revealed a significant difference between youth with ASD and youth with CD. Youth with ASD displayed higher activation in the anterior insula for angry faces than those with CD. The anterior insula plays an important role in affective processes and social behavior functioning (Benarroch, 2019; Y. Zhang et al., 2019) and, since functional and structural abnormalities in the insula have been consistently found in youth with CD (Fairchild et al., 2019a; Raschle et al., 2015), youth with ASD were expected to show higher insula activation compared to youth with CD. When controlling for mouth and eye fixations in angry facial expressions, the cluster size of insula activation was reduced, suggesting an association between gaze behavior and brain activation during facial emotion processing. This is supported by post-hoc results suggesting that differences in insula activation may be particularly linked to fixations to the mouth region in the ASD group (supplementary table 3). However, even though the cluster size was reduced when controlling for gaze behavior, the group difference was still significant suggesting that differences in brain activation during facial emotion processing go beyond the influence of gaze behavior.

However, this study has some limitations. Brain imaging results are tentative and thus, should be interpreted with caution. It is also important to note that only those with high functioning autism or Asperger's syndrome were recruited for intelligence comparability reasons between the groups. This subgroup's results thus, do not represent the complete heterogeneity of the ASD spectrum and cannot be easily generalized. This also extends to the limited generalizability of the heterogeneity in CD. Additionally, the task design did not include positive emotions and potential eye gaze differences for positive facial expressions (e.g. happy) could not be measured. Imputations were conducted to account for the missing data in the parent reported CBCL and ICU questionnaires due to difficulties to reach the parents or primary caregivers, especially in the CD group of which a large proportion were placed separately from their parents.

## 5. Conclusion

Youth with ASD and youth with CD showed different atypical gaze behavior patterns compared to healthy controls, which suggest that different mechanisms underpin the atypical facial emotion processing in these groups. Brain imaging results showed that gaze behavior is associated with differences in brain activation in the insula and may partially influence brain activation differences

among groups. Therefore, targeting attention to salient social cues in mouth or eye regions could potentially be beneficial in treatment interventions for disorders with facial emotion processing deficits.

**Conflict of interest statement**

The authors have declared that they have no competing or potential conflicts of interest.

**Acknowledgements**

The authors thank all adolescents, families, institutions and professionals who participated in the study. This study and AT were supported by the Swiss National Science Foundation (Grant no. 100014_185408/1).

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## *3. Study 2: Empathy deficits, callous-unemotional traits and structural underpinnings in autism spectrum disorder and conduct disorder youth*

Antonia Tkalcec*[1], Maria Bierlein*[1], Gudrun Seeger-Schneider[2], Susanne Walitza[2], Bettina Jenny[2], Willeke M. Menks[3,4], Lynn V. Felhbaum[5], Reka Borbas[5], David M. Cole[6], Nora Raschle[5], Evelyn Herbrecht[1], Christina Stadler†[1], Ana Cubillo†[1]

1- Child and Youth Psychiatry, University Psychiatric Clinic, Basel, Switzerland
2- Child and Youth Psychiatry, Psychiatric University Clinic, University of Zurich, Zurich, Switzerland
3- Donders Institute for Brain, Cognition and Behaviour, Radboud University, and Radboud University Medical Centre, Nijmegen, the Netherlands
4- Max Planck Institute for Psycholinguistics, Nijmegen, the Netherlands
5- Jacobs Center for Productive Youth, University of Zurich, Zurich, Switzerland
6- Translational Psychiatry, University Psychiatric Clinic, Basel, Switzerland

*AT and MB should be considered joint first author

†CS and AC should be considered joint senior author

**Abstract**

Distinct empathy deficits are often described in patients with conduct disorder (CD) and autism spectrum disorder (ASD) yet their neural underpinnings and the influence of comorbid Callous-Unemotional (CU) traits are unclear. This study compares the cognitive (CE) and affective empathy (AE) abilities of youth with CD and ASD, their potential neuroanatomical correlates, and the influence of CU traits on empathy. Adolescents and parents/caregivers completed empathy questionnaires (N=148 adolescents, mean age=15.16 years) and T1 weighted images were obtained from a subsample (N=130). Group differences in empathy and the influence of CU traits were investigated using Bayesian analyses and Voxel-Based Morphometry with Threshold-Free Cluster Enhancement focusing on regions involved in AE (insula, amygdala, inferior frontal gyrus and cingulate cortex) and CE processes (ventromedial prefrontal cortex, temporoparietal junction, superior temporal gyrus, and precuneus). The ASD group showed lower parent-reported AE and CE scores and lower self-reported CE scores while the CD group showed lower parent-reported CE scores than controls. When accounting for the influence of CU traits no AE deficits in ASD and CE deficits in CD were found, but CE deficits in ASD remained. Across all participants, CU traits were negatively associated with gray matter volumes in anterior cingulate which extends into the mid cingulate, ventromedial prefrontal cortex, and precuneus. Thus, although co-occurring CU traits have been linked to global empathy deficits in reports and underlying brain structures, its influence on empathy aspects might be disorder specific. Investigating the subdimensions of empathy may therefore help to identify disorder-specific empathy deficits.

**Lay summary.** To improve our understanding of empathy deficits in autism spectrum disorder (ASD) and conduct disorder (CD) youths, we measured the main empathy aspects affective (AE) and cognitive empathy (CE) using reports and underlying brain structures. While both disorders show overlapping empathy deficits, disorder-specificities can be found when accounting for the influence of co-occurring CU traits.

**Background**

Empathy is the ability to understand another person's mental state and respond with an appropriate emotion (Decety & Jackson, 2004), and is essential to social functioning (de Vignemont & Singer, 2006; de Waal & Preston, 2017; Eisenberg et al., 2014; Uzefovsky & Knafo-Noam, 2016; Walter, 2012). Affective (AE) and cognitive (CE) empathy are described as the two main aspects of empathy (Dvash & Shamay-Tsoory, 2014; Walter, 2012). AE is the ability to feel another person's emotion and respond with an appropriate emotional reaction (Baron-Cohen & Wheelwright, 2004) and includes experiencing personal distress due to the distress of others (Eisenberg, 2010; Uzefovsky & Knafo-Noam, 2016). CE includes Theory of Mind (TOM) or perspective taking (Uzefovsky & Knafo-Noam, 2016) and comprises the accurate recognition, understanding, and mentalization of the emotions and cognitions of others (Baron-Cohen & Wheelwright, 2004). Adaptive social behavior requires the interplay between AE and CE processes, with deficits in one of these aspects potentially leading to substantial impairments in social behaviors (Preckel et al., 2018).

Selective impairments in AE and CE have been observed in different psychological disorders such as patients with autism spectrum disorder (ASD) or conduct disorder (CD). Empathy deficits are a known core feature of ASD experiencing major difficulties in perspective-taking (Vilas et al., 2021), TOM (Baron-Cohen et al., 1985; Blair, 2005; Cantio et al., 2016; Happé et al., 2017; Jones et al., 2010; Schwenck et al., 2012) and social interaction (Frith & Frith, 2003; van der Zee & Derksen, 2020). Patients with ASD frequently show difficulties in emotion recognition and distinguishing between positive and negative facial expressions, which might lead to deficits in appropriate social responding and social reciprocity (Frith, 2001; Schulte-Rüther et al., 2017). Theories like the Empathy Imbalance (K. Rogers et al., 2007; Schwenck et al., 2012; Smith, 2006, 2009) suggest that youth and adults with ASD (Gillespie-Lynch et al., 2017; Lombardo et al., 2016; K. Rogers et al., 2007; Schwenck et al., 2012; Shalev et al., 2022; Smith, 2006, 2009), and neurotypicals with elevated autistic traits (Shalev & Uzefovsky, 2020) would display deficits in understanding others' emotions (CE) and a surfeit in AE, while others suggest a more global empathy deficit including AE and CE (Grove et al., 2014). By contrast, the available evidence for youth with CD suggests that AE would be impaired while CE is not (Blair, 2013; Blair et al., 2014; Igoumenou et al., 2017). Children and youth with CD are typically characterized by repetitive and persistent behaviors of violations of others' rights, theft, lying, violence, and reckless breaking of rules (American Psychiatric Association, 2013; Frick & Nigg, 2012). CD poses a significant burden at the individual, social and economic levels (Erskine et al., 2014, 2016; Foster et al., 2005). It also

presents heightened risks for comorbid disorders (Angold et al., 1999; Erskine et al., 2016; Foster et al., 2005; Loeber et al., 2009; Odgers, 2009), which often persists into adulthood (Fairchild et al., 2019; Simonoff et al., 2004). Youth with CD and high callous-unemotional (CU) traits show a distinctive developmental pathway (Frick & Kemp, 2021) typically displaying more severe, aggressive, and persistent antisocial behaviors (Fontaine et al., 2011; Frick et al., 2003; Lawing et al., 2010; McMahon et al., 2010; Waller & Hyde, 2018; Willoughby et al., 2014). CU traits, defined by low empathy, guilt, and prosociality (Fairchild et al., 2019), have been associated with AE and empathy deficits in relation to antisocial and psychopathic behaviors (Burghart & Mier, 2022; Campos et al., 2022; Jones et al., 2010; Martin-Key et al., 2017; Waller et al., 2015), and are considered a risk factor for the development of psychopathy in adulthood (Hyde & Dotterer, 2022). Some evidence suggests the potential presence of a double dissociation in the CE/AE empathy deficits observed in ASD and CD adolescents with high CU traits, respectively (Chen et al., 2016; Jones et al., 2010; Lockwood et al., 2013; Pijper et al., 2016; Schwenck et al., 2012). However, a recent meta-analysis did not observe differences in association strength between CU traits and AE or CE (Waller, Wagner, et al., 2020) implying that CU traits might rather be linked with global empathy. Interestingly, although CU traits have been primarily linked to CD, CU traits and ASD are both characterized by disruptive behaviors and reduced empathic responsiveness (American Psychiatric Association, 2013), and often co-occur in children with ASD (Carter Leno et al., 2021). Thus, CU traits might present a potential symptomatic overlap between ASD and CD (Carter Leno et al., 2015, 2021; Frick et al., 2013; Herpers et al., 2016; Ibrahim et al., 2019; Kaat & Lecavalier, 2013). An improved understanding on the association between CU traits and the empathy deficits observed in ASD and CD and could potentially help would be needed to test whether these deficits really show a double dissociation character (Georgiou et al., 2019; Grove et al., 2014; Klapwijk et al., 2016; Noppari, 2022; Vilas et al., 2021).

Brain imaging studies have shown CE processes to be more strongly supported by cortical regions whereas AE processes would be supported by neural networks with more significant involvement of subcortical and limbic regions (Bernhardt & Singer, 2012; Bray et al., 2022; Bzdok et al., 2012; Fan et al., 2011; Frith & Frith, 2003; Lamm et al., 2011; Schurz et al., 2014; Stern et al., 2019; Uribe et al., 2019; Van Overwalle & Baetens, 2009). Thus, taking the neural correlates of a potential double dissociation in empathy deficits into account, ASD would be expected to show neural abnormalities in cortical regions involved in CE processes, and youth with CD in subcortical and limbic regions involved in AE processes. The evidence is however inconsistent (Klapwijk et al., 2016; Noppari, 2022). In a recent meta-analysis, ASD youth displayed gray matter volume

(GMV) decreases in limbic regions including temporal cortex and amygdala, linked to processes underlying AE (Marsh, 2018), compared with typically developing youth (TD) (Del Casale et al., 2022). Youth with CD have meanwhile shown reduced GMV across cortical regions including the anterior cingulate cortex (ACC), ventromedial prefrontal cortex (vmPFC), temporal cortex and anterior Insula (AI), as well as subcortical structures (Fairchild et al., 2019; J. C. Rogers & De Brito, 2016; Sebastian et al., 2016). The precise contribution of these regions to the observed empathy deficits is yet to be determined (Fan et al., 2011; Gothard, 2020; Mutschler et al., 2013; Šimić et al., 2021; Walter, 2012). Compared to healthy participants, adults who were criminal offenders with psychopathic traits displayed lower GMV in the insula, frontal cortex and sensorimotor cortex while adults with ASD showed reduced GMV in left precuneus (PCu) and cerebellum (Noppari, 2022). Furthermore, both groups shared structural alterations in the right precentral gyrus compared with a healthy control group, which has been linked to AE processes (Bray et al., 2022; Kim et al., 2020; Naor et al., 2020). In direct comparisons, the offender group showed lower GMV in the left temporal pole and left inferior frontal gyrus (IFG) than the ASD group (Noppari, 2022). These results therefore suggest the potential presence of both shared and disorder-specific and shared structural differences underlying AE and CE deficits shown by patients with ASD and patients with psychopathic traits. These results would be in line with findings in a comparison study on brain function revealing shared reduced responses during an emotion contagion task, which is linked to AE, in the amygdala, but differ in their functional alterations from controls during an emotion recognition task, linked to CE processes (Klapwijk et al., 2016).

Differences linking specific empathy deficits to structural neural correlates in youth with ASD or CD have not yet been investigated. The direct comparison of potential disorder-specific differences in brain structure and their association with empathy deficits in neurodevelopmental disorders acquires particular relevance during adolescence. This is due to the crucial neural developmental processes that still undergoing during this period. Together with pubertal changes and potential stressors related among others to social factors, this makes of adolescence a period of particular vulnerability to the appearance or exacerbation of psychiatric symptoms (Blakemore, 2012; Di Martino et al., 2014; Dumontheil, 2016; Fuhrmann et al., 2015).

In sum, the specificity of the empathy deficits observed in ASD and CD and their underlying brain structural correlates are not yet well understood. Such studies might provide additional insight into differences between CD and ASD in AE/CE measured as a trait and might help to close the knowledge gap on the disorders' neurodevelopmental specificities. This might

help in defining overlapping and distinctive empathy aspects and disorder-specific deficits which might consequently support efforts towards a consensus in the empathy concept definition. Additionally, the compared influence of CU traits on possible associations of reported measures and brain structures in both ASD and CD has not yet been investigated.

This study investigates the potential dissociation in empathy deficits in youths with CD and ASD and their neuroanatomical underpinnings expecting that CU traits show a stronger impact on the CD than ASD group based on its primary link to this disorder (American Psychiatric Association, 2013). We used measures from self- and parent-reports to overcome the limitation of previous studies investigating empathy mainly using either parent-or caregiver-reports for children or self-reports for adolescents (Sesso et al., 2021). Additionally, we use structural brain imaging to identify the potential differences in neural structures underlying the empathy deficits observed in these populations. We hypothesize that, compared with TD, patients with CD display lower scores in AE and lower GMV in regions involved in AE processes (CD<ASD, TD), while patients with ASD show lower scores in CE and lower GMV in regions involved in CE processes (ASD<CD, TD). We also want to determine to what extent CU traits are related to AE and/or CE and associated brain structures in CD and ASD and whether there are group differences in this association.

## 2. Methods

### 2.1 Participants

Adolescent participants with ASD and CD were recruited from different specialized clinical settings and residential centers in Basel and Zurich (University Psychiatric Clinic in Basel, Psychiatric University Clinic in Zurich, AHBasel foundation, and youth home Schlössli in Basel). Participants included in the TD group were recruited from socioeconomically diverse secondary schools in the Canton Basel-Stadt. Inclusion criteria for children and adolescents within the patient's group were the fulfillment of the DSM-5 diagnostic criteria (American Psychiatric Association, 2013) for either CD or ASD and no comorbid depressive or anxiety disorder. To be included in the TD group, participants could not meet the criteria for any current or previous psychiatric disorder. Clinical assessment of the diagnostic criteria was conducted using a semi-structured clinical interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version, K-SADS-PL) (Kaufmann et al., 1997) for all participants. For the ASD group, the ADOS or ADI-R (Bölte et al., 2006; Poustka et al., 2015) was additionally administered. Additional inclusion criteria were an average IQ score (>70) for all participants. Consequently, this entailed that for the ASD group diagnostic criteria for either Asperger's

syndrome or high functioning autism had to be fulfilled. When IQ test results were available from the clinics which were no older than 24 months prior to study enrollment, then information was entered into our database. When such information was not available or results were older than 24 months, a psychometric IQ assessment using Wechsler Intelligence Scale For Children (WISC-IV) (Wechsler, 2012b) or Wechsler Adult Intelligence Scale (WAIS-IV) (Wechsler, 2012a) was conducted. Participants and caregivers/parents filled out different questionnaires. Participants completed the Basic Empathy Scale (BES) (Jolliffe & Farrington, 2006), whereas parents/ caregivers completed the Griffith Empathy Measure (GEM) (Dadds et al., 2008). Both questionnaires provide subscale scores of AE and CE. In addition, caregivers filled out the Inventory of Callous Unemotional traits (ICU) (Frick, 2017). Participants then underwent a structural brain imaging data acquisition session. Written informed assent and/or consent was obtained from participants and caregivers. All procedures were conducted in accordance with the Declaration of Helsinki and approved by the local Ethics Committee (EKNZ, 2019-02386).

The total sample included 163 participants, with NCD = 76, NASD = 40, and NTD = 47. However, 15 participants had to be excluded due to missing data (NCD=7; NASD=7; NTD=1). Thus, the final sample with valid psychometric data consisted of 148 participants, with NCD = 69, NASD = 33 and NTD = 46 youth aged 10 to 18 years (M=15.24; SD=2.12 years). For the MRI analysis, data from 18 participants had to be additionally excluded due to missing/low-quality data or incidental findings (NCD=11, NASD=6, NTD=1). Thus, valid brain imaging data was available for a subset of 130 participants (NCD=58; NASD=27; NTD=45). Given that the data was collected in two waves with the first wave collecting data from a total of 61 participants (NCD=23; NASD=3; NTD=35) and the rest being collected in the second wave, we included data collection wave as an additional regressor of no interest in all questionnaire and brain imaging analyses to account for potential differences in the version of the MRI operating system and changes in the structure of the research team or other potential differences during data collection. Further details on the sample characteristics are shown in table 1.

*Table 1*. Sample characteristics

| | **ASD (N=33)** | | **CD (N=69)** | | **TD (N=46)** | | *Chi squar e/F Stat* | *p value* |
|---|---|---|---|---|---|---|---|---|
| | *Mean (SD)/ Count (%)* | *NR missing values* | *Mean (SD)/ Count (%)* | *NR missing values* | *Mean (SD)/ Count /%)* | *NR missing values* | | |
| Sex | 12F/21M | 0 | 16F/53M | 0 | 23F/23M | 0 | 8.85 | 0.01 |
| Age (Years) | 14.97 (2.57) | 0 | 15.61 (1.81) | 0 | 14.89 (2.16) | 0 | 1.96 | 0.15 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| IQ | 106.24 (14.21) | 0 | 96.78 (11.08) | 4 | 103.46 (8.27) | 4 | 9.79 | <0.001 |
| AE GEM | -5.97 (15.61) | 1 | 1.29 (13.44) | 24 | 1.96 (11.92) | 2 | 4.01 | 0.02 |
| CE GEM | 0.52 (10.06) | 1 | 5.14 (9.19) | 24 | 10.85 (8.29) | 2 | 12.74 | < 0.001 |
| Total GEM | -2.91 (27.61) | 1 | 15.19 (24.63) | 24 | 23.28 (22.87) | 2 | 10.96 | <0.001 |
| AE BES | 34.42 (7.83) | 1 | 34.22 (6.17) | 3 | 38 (6.51) | 4 | 4.93 | 0.01 |
| CE BES | 30.36 (7.33) | 1 | 36.29 (5.29) | 3 | 36.78 (4.07) | 4 | 15.83 | <0.001 |
| Total BES | 63.79 (13.87) | 1 | 70.55 (9.47) | 3 | 74.98 (9.01) | 4 | 10.97 | <0.001 |
| ICU sum | 28.33 (10.60) | 1 | 28.84 (9.29) | 23 | 17.07 (8.06) | 2 | 25.05 | <0.001 |
| ADHD | 7 (21.21%) | 0 | 30 (43.48 %) | 0 | 0 | 0 | 28.15 | <0.001 |
| ODD | 2 (6.06%) | 0 | 12 (26.08 %) | 0 | 0 | 0 | 18.09 | <0.001 |
| Addictive disorders | 0 | 0 | 19 (27.54%) | 0 | 0 | 0 | 24.96 | <0.001 |
| PTSD | 2 (6.06%) | 0 | 15 (21.74%) | 0 | 0 | 0 | 14.06 | <0.001 |
| Tic | 1 (3.03%) | 0 | 1 (1.45%) | 0 | 0 | 0 | 1.33 | 0.51 |
| Bulimia Nervosa | 0 | 0 | 1 (1.45%) | 0 | 0 | 0 | 1.15 | 0.56 |

This table shows the mean and standard deviation (SD) or number count and percentage (%) for each group as well as the group differences for the key demographic variables and questionnaire scores utilized in the present study. For each variable and within each group, the number of participants with missing values for the corresponding value is shown. Missing values were imputed using the MICE package in R with 5000 imputations using all available data for those participants used in the present study. Group comparisons were conducted after imputation and do not differ from those before the imputation. Except for age, comorbid Tic disorders and Bulimia Nervosa, at least one group differed significantly in all other variables. *ASD = Patients with autism-spectrum disorder diagnosis, CD = Patients with conduct disorder diagnosis, TD = Typically developing youth, IQ = intelligence quotient (total score of WASI, WISC or WAIS), AE/CE GEM= affective/cognitive empathy subscale sum of the Griffith Empathy measure (GEM), AE/CE BES = affective/cognitive empathy score of the Basic Empathy Scale, Total GEM/BES = total sum score of the Griffith Empathy Measure/Basic Empathy Scale, ICU sum = total sum score of Inventory for Callous Unemotional traits (ICU) (Frick, 2017), ADHD =Attention Deficit Hyperactivity Disorder, ODD = Oppostional Defiant Disorder, Addictive disorders = Substance or alcohol*

*abuse/dependency disorder, PTSD = Post-traumatic Stress Disorder, Tic = Tic disorders.*

2.2 Analysis of self-and parent-reported empathy questionnaires

All behavioral analyses were conducted using R (Version 4.2.1) (R Core Team, 2020) and RStudio (Version 2022.7.0.547) (RStudio Team, 2022). From the whole dataset, 5% of participants did not have a valid record of IQ data, 5% of participants had missing responses in the BES questionnaire, 18% in the GEM questionnaire, and 17% in the ICU questionnaire. Following standard recommendations, imputation of missing data is practicable for variables missing at random, using the "mice" package to implement multiple imputation by chained equations (Buuren & Groothuis-Oudshoorn, 2011) (m = 100, maxit = 20, meth = "pmm") to maximize the data used for those analyses. Details on the missing data for each variable are shown in table 1.

We examined the presence of group differences in the affective and cognitive subscales of the BES and GEM using four regression models within a Bayesian framework, with the group values entered as the main regressor of interest and empathy scores as the dependent variables. Age, sex, IQ, and data collection wave were also included as regressors of no interest to account for potential developmental and group differences in these dimensions. All variables were z-scored before being entered in the analyses. The regression included a flat prior and a Gaussian likelihood distribution, with parameters warmup = 1000, iter = 2000, 3 chains, and 3 cores. Since CU traits have shown to be significantly negatively correlated with empathic abilities, especially in antisocial youth (Waller, Wagner, et al., 2020) two additional separate models were created including CU traits either as a regressor or in interaction with the variable group. For this, z-scores were calculated from the total sum score of the Inventory of Callous Unemotional traits (ICU) (Frick, 2017). Then, all three models were compared using the leave-one-out cross validation (LOO) method, which uses the log-likelihood computed by n (as size of the dataset) posterior simulations with one sample as the test set and the rest being the training set for the model (Vehtari et al., 2017).

2.3 Structural MRI acquisition and analyses

Brain structural images were acquired using a Siemens 3.0 Tesla Prisma scanner at the University Hospital Basel. The acquired T1-weighted structural magnetization prepared rapid gradient echo (MPRAGE) images included 192 slices, field of view 256mm, voxel size 1x1x1mm, repetition time 1900ms, echo time 3.42ms. Customized TPMs and DARTEL templates to represent the whole sample were generated within the Cerebromatic toolbox (COM) (Wilke et al., 2017), an updated version of TOM8 using a more flexible approach (Wilke et al., 2017). Therefore,

information about age, sex, and field strength of the 130 participants was used to create priors of the population of interest based on the regression parameters provided by the University of Tuebingen.

In line with previous studies (Del Casale et al., 2022; Fairchild et al., 2019; Noppari, 2022; J. C. Rogers & De Brito, 2016; Sebastian et al., 2016), GMV was used as brain structural measure as it takes into account influences of cortical volume subcomponents such as cortical thickness or surface areas (Vijayakumar et al., 2018) including their different developmental trajectories (Mills et al., 2016). Thus, GMV allows us to relate the findings with the available evidence in the literature. Voxel-Based Morphometry (Ashburner & Friston, 2000) analysis was conducted using CAT12 (Computational Anatomy Toolbox) (Gaser & Dahnke, 2016), implemented in SPM12 (Statistical Parametrical Mapping) (Penny et al., 2006). After individual inspection of raw data, preprocessing was conducted following the standard steps as recommended in the CAT2 manual. Next, we manually inspected the quality reports by CAT12, (providing parameters of noise, inhomogeneities, and image resolution) for each T1 image. Only those individuals whose data quality was classified as C- or higher were included in the analyses, representing satisfactory image quality (https://neuro-jena.github.io/cat/index.html#QC). Consequently, N = 3 participants had to be excluded due to quality issues. To correct for differences in brain size and volume, Total Intracranial Volumes (TIV) were calculated for each participant with CAT12 and added to the analyses as a regressor of no interest.

### 2.4 Region of Interest (ROI) statistical analyses

To investigate the association and potential group differences between GMV and AE and CE, we created two general linear models for the GEM and the BES, including group as factor and both empathy subscales as regressors. The simultaneous consideration of both empathy subscales differs from the analyses in 2.2 and is justified by previous separate analyses whose results did not differ from the present one. Next, two additional models were created to investigate the potential associations between CU traits and GMV, by adding ICU total scores as an additional regressor to the previous models. Further models were designed to examine group differences in the association between empathy respectively CU traits and GMV (group x empathy; group x CU), as well as the interaction of CU traits and empathy associated with GMV (CU x empathy), with the product of empathy and CU trait scores as a new regressor. Separate interaction models were created with each of them including both empathy subscales for the corresponding questionnaire. For all models, the normalized individual images were included in a full factorial anova, with IQ, age, sex and TIV

as regressors of no interest. As described in section 2.1, an additional regressor was included to account for potential differences related to the data collection wave. We restricted the analyses to regions previously associated with CE and AE (Bray et al., 2022; Fan et al., 2011; Schurz et al., 2014; Stern et al., 2019). To do so, we created a combined mask of regions associated with AE (amygdala, insula, IFG, cingulate cortex), and CE processes (vmPFC, TPJ, superior temporal gyrus, and PCu), using FSL eyes (Version 1.3.0) (https://zenodo.org/record/7038115#.Y9Kly8hKiUc) choosing from the Harvard Oxford Atlas, and xjView (Version 10.0) (https://www.alivelearn.net/xjview/) (Supplementary Figure 1). Significant results at $p<0.05$ were identified via the generation of a null distribution over 5,000 permutations, followed by a Threshold-Free Cluster Enhancement (TFCE) technique along with family-wise error (FWE) correction for comparison across multiple voxels. TFCE identifies cluster-like patterns by considering voxel- and cluster-related information without relying on fixed statistics for cluster-definition thresholds, thus computing significant clusters that retain voxel-wise weightings (Smith & Nichols, 2009).

## 3. Results

Construct evaluation

Spearman correlations were conducted in R to identify the underlying correlations between the corresponding subscales of the two questionnaires (i.e., cognitive subscale in the self-report and cognitive subscale in the parent-report questionnaire). Each empathy subscale of the self-report showed a small correlation with each of the counterpart subscales of the parent-report (CE in BES x GEM: rho = .16, p = .05; AE in BES x GEM: rho = .25, p <.001) (Supplementary Table 1a). To further investigate potential differences in this matter between groups, correlations were conducted for each of the groups separately. Results display low correlations for AE (rho>.3, p<.001) in the ASD and the TD group and non-significant correlations for AE in the CD group (Supplementary Table 1b). Non-significant CE correlations were found between questionnaires across all groups (Supplementary Table 1b).

### 3.1 Questionnaire results

Multiple linear regressions within a Bayesian framework without CU traits included in the models revealed significant results for the variable group in most combinations of empathy and questionnaire type (Table 2). In the self-report (BES), the ASD group reported significantly lower scores in CE compared to the TD and CD groups while no significant difference was found between the CD and TD group (Table 2). In the parent-report (GEM), the ASD group showed lower AE and

CE scores than the TD and CD groups and the CD group displayed lower CE scores than the TD group. Model comparisons revealed that the majority preference lies with the models that include CU traits as a covariate (Table 3). However, a better model fit cannot be completely determined because of low standard errors. Although the interaction of group and CU traits was the preferred model in the parent-reported CE subscale (GEM), this was not the case for parent-reported AE (GEM) and self-reported AE and CE (BES) (Table 3). With the inclusion of CU traits as a covariate in the models, the CD group no longer significantly differed from the TD group in parent-reported CE. For patients with ASD, group differences were reduced for AE in the parent-report but remained for CE in both self-and parent-reports (Table 4). Additional supplementary analyses were conducted including the interactions of group and CU traits (Supplementary Table 2), age (Supplementary Table 3), sex (Supplementary Table 4), and discrepancy measures for both empathy questionnaires (Supplementary Table 5). Results showed negative main effects of sex on self-reported AE, and main and interaction effects on AE discrepancy measures. Age and group revealed a positive interaction effect for the ASD group in self-reported AE.

*Table 2*. Bayesian regression analysis for self- and parent-reports on AE/CE

| | Self-report | | | | | Parent-report | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Affective Empathy | | | | | | | | | |
| *Hypothesis* | *Est.* | *SE* | *95% CI* | | *Post. Prob.* | *Est.* | *SE* | *95% CI* | | *Post. Prob.* |
| ASD<TD | -0.15 | 0.25 | -0.56 | 0.25 | 0.27 | -0.46 | 0.27 | -0.9 | -0.03 | 0.04 |
| CD<TD | -0.24 | 0.19 | -0.56 | 0.07 | 0.1 | -0.05 | 0.22 | -0.41 | 0.3 | 0.6 |
| ASD>CD | 0.1 | 0.22 | -0.26 | 0.46 | 0.33 | -0.5 | 0.25 | -0.91 | -0.11 | 0.02 |
| | Cognitive Empathy | | | | | | | | | |
| *Hypothesis* | *Est.* | *SE* | *95% CI* | | *Post. Prob.* | *Est.* | *SE* | *95% CI* | | *Post. Prob.* |
| ASD<TD | -0.92 | 0.24 | -1.31 | -0.53 | 0 | -1.11 | 0.24 | -1.51 | -0.71 | 1 |
| CD<TD | -0.06 | 0.2 | -0.37 | 0.27 | 0.39 | -0.57 | 0.19 | -0.88 | -0.25 | 0 |
| ASD<CD | -0.85 | 0.22 | -1.21 | -0.49 | 0 | -0.54 | 0.23 | -0.92 | -0.17 | 0.01 |

This table shows the multiple regression analysis results testing the one-sided hypotheses on key dependent variables: AE and CE subscale scores of self-reports (BES) (Joliffe & Farrington, 2006) and parent-reports (GEM) (Dadds et al., 2008). All models included the following regressors: group, age, IQ, sex, data collection wave. The variable CU traits was created using z-scores of the total sum of the Inventory of Callous Unemotional traits (ICU) (Frick, 2017). All included variables were z-scored. Results show lower CE/AE scores for the ASD group compared to the TD group in the parent-report. Compared to the CD group, the ASD group shows lower CE scores in self-and

parent-reports, and lower AE scores in the parent-report. The CD group shows lower CE scores in the parent-report when compared to the TD group. *Est. = Estimate, SE = Standard-Error, 95% CI = Credible interval, Post. Prob = Posterior Probability under the hypothesis against the hypothesis' alternative. Hypothesis = direction of tested hypothesis, ASD = youth with autism spectrum disorder, CD = youth with conduct disorder, TD = typically developing youth*

*Table 3.* Model comparison using leave-one-out cross validation method among models with and without CU traits as covariate and in interaction with group

| Affective Empathy | | | | | |
|---|---|---|---|---|---|
| *Model* | *elpd_diff* | *se_diff* | *Model* | *elpd_diff* | *se_diff* |
| CU as cov. | 0 | 0 | CU as cov. | 0 | 0 |
| Basic model | -1.7 | 2.1 | Interaction CU x Group | -0.6 | 1.9 |
| Interaction CU x Group | -2 | 1.1 | Basic model | -1.8 | 2.8 |
| Cognitive Empathy | | | | | |
| *Model* | *elpd_diff* | *se_diff* | *Model* | *elpd_diff* | *se_diff* |
| CU as cov. | 0 | 0 | Interaction CU x Group | 0 | 0 |
| Basic model | -0.6 | 2.2 | CU as cov. | -0.6 | 2 |
| Interaction CU x Group | -1.8 | 1.2 | Basic model | -6.1 | 4 |

This table shows the model comparison results of leave-one-out cross validation as information criteria on key dependent variables of the multiple regression analysis: AE and CE subscale scores of self-reports (BES, Jolliffe & Farrington, 2006) and parent-reports (GEM, Dadds et al., 2008). The basic model *(=Basic model)* included the following regressors: group, age, IQ, sex and data collection wave. Additionally, one model included CU traits as covariate *(=CU as cov.),* and another model an interaction of CU traits and group *(=Interaction CU x group)*. The variable CU traits was created using z-scores of the total sum of the Inventory of Callous Unemotional traits (ICU) (Frick, 2017). All included variables were z-scored. Results show the pairwise comparisons between each model and the model with the largest ELPD. The preference lies with the model including CU traits as covariate in the model for AE subscale scores of self-and parent-reports and CE subscale scores of the self-reports. For CE, in the parent-report the model including the interaction of CU traits and group is preferred over the other models. *elpd diff = expected log pointwise predictive density, se diff= standard error, CU = Callous-Unemotional traits.*

*Table 4*. Bayesian regression analysis for self - and parent-reports on AE/CE including CU traits as regressor in the model

| | Self-report | | | | | Parent-report | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Affective Empathy | | | | | | | | | |
| *Hypothesis* | *Est.* | *SE* | *95% CI* | | *Post. Prob.* | *Est.* | *SE* | *95% CI* | | *Post. Prob.* |
| ASD<TD | 0.04 | 0.26 | -0.4 | 0.46 | 0.56 | -0.22 | 0.28 | -0.68 | 0.23 | 0.22 |
| CD<TD | -0.05 | 0.21 | -0.4 | 0.29 | 0.41 | -0.3 | 0.22 | -0.68 | 0.07 | 0.92 |
| ASD>CD | 0.09 | 0.21 | -0.25 | 0.44 | 0.34 | -0.51 | 0.23 | -0.9 | -0.13 | 0.01 |
| | Cognitive Empathy | | | | | | | | | |
| *Hypothesis* | *Est.* | *SE* | *95% CI* | | *Post. Prob.* | *Est.* | *SE* | *95% CI* | | *Post. Prob.* |
| ASD<TD | -0.73 | 0.26 | -1.15 | -0.31 | 0 | -0.78 | 0.25 | -1.19 | -0.37 | 1 |
| CD<TD | 0.12 | 0.21 | -0.22 | 0.46 | 0.72 | -0.23 | 0.21 | -0.56 | 0.11 | 0.13 |
| ASD<CD | -0.86 | 0.22 | -1.22 | -0.51 | 0 | -0.57 | 0.22 | -0.92 | -0.2 | 0.01 |

This table shows the multiple regression analysis results testing the one-sided hypotheses on key dependent variables: AE and CE subscale scores of self-reports (BES) (Joliffe & Farrington, 2006) and parent-reports (GEM) (Dadds et al., 2008). All models included the following regressors: group, age, IQ, sex, data collection wave and CU traits. The variable CU traits was created using z-scores of the total sum of the Inventory of Callous Unemotional traits (ICU) (Frick, 2017). All included variables were z-scored. Results show group differences in the CE aspects for both self- and parent-reports with the ASD group showing lower scores compared to the TD and CD group. Both CD and ASD groups do not significantly differ in AE scores from the TD group, but the ASD group shows lower scores than the CD group in parent-reported AE. *Est. = Estimate, SE = Standard-Error, 95% CI = Credible interval, Post. Prob = Posterior Probability under the hypothesis against the hypothesis' alternative. ASD = youth with autism spectrum disorder, CD = youth with conduct disorder*

### 3.2. Structural MRI Results

Within the regions of interest, we observed no significant group effects or effects of AE or CE on GMV in either of the two models including group as factor and both empathy scales of either the GEM or the BES and regressors. The two models that additionally included the ICU score as regressor, however, revealed significant negative associations with GMV for both questionnaires GEM and BES with overlapping clusters in the left ACC extending into mid-cingulate (MCC) and

the vmPFC, and PCu (peak MNI = 3; 31; -15, 32457mm3 volume), with all p(FWE) <.05 (Figure 1, Table 5). Significant clusters for both models including either empathy scores of the BES or the GEM do not substantially differ between them. Separate results for both models are displayed in supplementary table 6. No significant interaction effect was observed. For completeness, we conducted whole brain analyses (Supplementary Figure 2) whose results do not differ significantly from the main ROI described above with exception of the additional cluster in the orbitofrontal pole, that was negatively associated with CU traits in the BES (Supplementary Figure 2 and Supplementary Table 7). An additional region of interest analysis of GMV was conducted to examine possible structural differences in youths with low versus high levels of CU traits based on the clinical cutoff score of 30 in the ICU questionnaire, as recommended by Docherty et al. (2017), with TD participants as a separate group (Supplementary Figure 4, Supplementary Table 8). Significant group differences were found between the high CU group, the low CU group, and the TD group. Especially, the high CU group (>30) showed lower GMV in the ACC/MCC, vmPFC and PCu, and additionally, in the amygdala, hippocampus, and insula than the TD group.

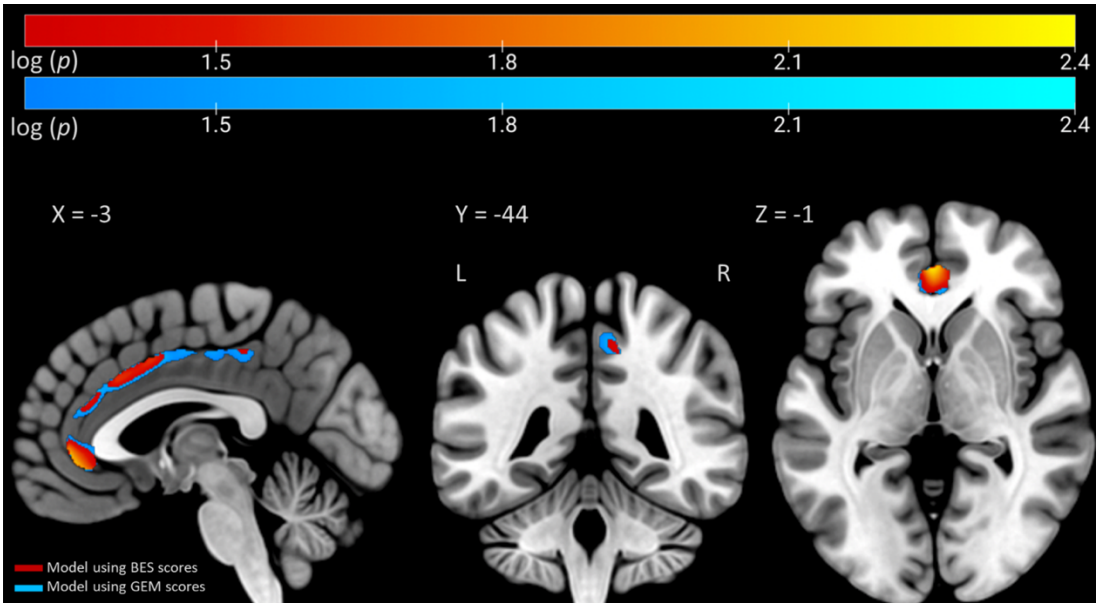


*Figure 1.* This figure shows the overlap of the full factorial analyses results including AE and CE of either the BES or GEM, CU traits and group as regressors of interest and TIV, age, sex, data collection wave and IQ as regressors of no interest. Colored clusters depict the voxels significantly negatively associated with CU traits, with blue clusters representing results from the model including empathy scores of the GEM, while red clusters depict results of the model including empathy scores of the BES. Across all participants, significant associations were observed between GMV and CU traits in the left ACC, extending into the MCC and vmPFC, as well as the PCu.

Results for both models do not differ substantially from each other. (peak MNI = 3;31;-15, 32457mm3 volume), with all p(FWE) < 0.05. *GMV = Gray Matter Volume, CU = Callous-Unemotional traits, BES = Basic Empathy Scale, GEM = Griffith Empathy Measure, AE = Affective Empathy, CE = Cognitive Empathy, TIV = Total Intracranial Volume, IQ = Intelligence Quotient, ACC = Anterior Cingulate Cortex, MCC = Mid Cingulate Cortex, vmPFC = ventromedial Prefrontal Cortex, PCu = Precuneus, MNI = Montreal Neurological Institute, FWE = Familywise Error rate*

*Table 5.* Spatial Centers of Gravity Depicting the Shared Peak Clusters of the Region of Interest Analysis Negatively Associated With Callous-Unemotional Traits

| Structures | Volume | Spatial Centers of Gravity | | |
|---|---|---|---|---|
| | | X | Y | Z |
| Medial orbitofrontal cortex (R), Anterior cingulate (L,R) | 1452 | 1 | 39 | -1 |
| Anterior cingulate (L), Mid-cingulate (L, R) | 1039 | -3 | 13 | 37 |
| Mid-cingulate (L) | 594 | -8 | -25 | 42 |
| Anterior cingulate (L,R) | 246 | -1 | 35 | 22 |
| Precuneus (R), Mid-cingulate (R) | 167 | 11 | -43 | 48 |

This table depicts the spatial centers of gravity of binary clusters significantly negatively associated with CU traits that were created by combining regions that were significant in both models. Regressions for the separate models included group as factor, AE and CE of either the self-reported BES or the other-reported GEM, and total CU trait scores as regressors, as well as IQ, age, sex, data collection wave, and TIV as covariates. All included variables were z-scored. Results were estimated using TFCE, FWE-corrected, and thresholded at $p < 0.05$. Across all participants and for both models, significant associations were observed between GMV and CU traits in the left ACC, extending into the vmPFC and the MCC, as well as the PCu. As can be seen in Supplementary Table 2 significant clusters for both models including empathy scores of either the BES or the GEM do not differ substantially from each other. *GEM = Griffith Empathy Measure, BES = Basic Empathy Scale, AE = Affective Empathy, CE = Cognitive Empathy, CU = Callous-Unemotional traits, IQ = Intelligence Quotient, TIV = Total Intracranial Volume, FWE = Family-Wise Error*

*correction for multiple comparisons, TFCE = Threshold Free Cluster Enhancement, MNI =Montreal Neurological Institute, R = Right, L = Left.*

## 4. Discussion

The aim of this study was to improve our understanding of the shared and disorder-specific deficits in AE and CE in youth with CD and ASD, as well as the underlying differences in brain structure. We furthermore explored the influence of co-occurring CU traits in these associations across all participants. Overall, our findings do not support a double dissociation of empathy deficits in youth with ASD and CD (Blair, 2013; Blair et al., 2014; Gillespie-Lynch et al., 2017; Igoumenou et al., 2017; Lombardo et al., 2016; K. Rogers et al., 2007; Schwenck et al., 2012; Shalev et al., 2022; Smith, 2006, 2009), but global empathy deficits for ASD in the parent-report and CE deficits in the self-report, and for CD, parent-reported CE deficits. Interestingly, when CU traits were included in the models, the observed influence of CU traits on empathy aspects was dependent on the disorder. Thus, compared with the TD group, the ASD group no longer showed AE deficits, while the CD group showed no longer CE deficits. Additionally, CU traits were negatively associated with GMV in left ACC extending into MCC and vmPFC, and PCu across all participants.

The potentially overlapping empathy deficits displayed by the group of youths with ASD and those with CD results would be in line with the overlapping aggressive, antisocial, and disruptive symptoms observed in ASD and CD, which were also associated with empathy deficits in previous studies (Frick et al., 2013; Kaat & Lecavalier, 2013). For the ASD group, global empathy deficits were observed, in line with the existing evidence of deficits in CE (K. Rogers et al., 2007; Schwenck et al., 2012; Vilas et al., 2021), but also in abilities that need both AE and CE (Lombardo et al., 2010) such as self-other distinction. Against expectations, CD youths only showed CE deficits in the parent-report and no deficits in the self-report, which might suggest differences between self-perceived and externally observed empathy abilities. Notably, a significant proportion of the parent-reports for CD youths was completed by the main caregivers from institutionalized settings. While the results are comparable to those from previous studies (Waller, Wagner, et al., 2020), it is conceivable that temporary caregivers might have a limited insight into each empathy aspect capacity of the respective adolescent.

Our results indicate that parent-reported CE deficits might be related to CU traits in CD youth but not in those with ASD, in line with previous studies (Waller, Wagner, et al., 2020), and with the potential disorder-specific character of CE deficits in ASD, which would remain significant beyond the presence of CU traits (Jones et al., 2010; Pijper et al., 2016). CU traits have

been associated with affective TOM, linked with CE and AE processes (Gao et al., 2019) and might thus be related to AE and the interplay of AE and CE processes, but not CE processes per se. In our study, the inclusion of CU traits in the computational models reduced the relevance of the AE but not CE deficits for the ASD group, suggestive of a potential differential impact of CU traits on empathy deficits on each disorder. These findings would help to understand those of previous studies where deficits in pure CE processes were found only in ASD samples and not in youth with high levels of CU traits (Jones et al., 2010; O'Nions et al., 2014; Schwenck et al., 2012; Vilas et al., 2021). This might further suggest that CE empathy deficits are influenced by other factors in youth with ASD than CD. Thus, CE deficits in ASD youth might be less influenced by CU traits in the social impairment of the disorder than in CD.

Structural brain imaging analyses did not reveal any regions significantly associated with potential differences in empathy aspects, groups, or their interaction. Thus, our results differ from previous evidence suggesting that AE/CE deficits are linked with distinct brain regions in CD and ASD youths (Banissy et al., 2012; Eres et al., 2015; Hoffmann et al., 2016; Klapwijk et al., 2016; O'Nions et al., 2014; von Polier et al., 2020). A key difference with previous brain imaging studies is the use of scores of empathy as trait and measures of brain structure, relative to the commonly used state-like measures of empathy and brain functional measures (Lamm et al., 2011; Moore et al., 2015). Negative associations were however observed between CU traits and GMV in the ACC/MCC, vmPFC, and PCu for both self- and parent-reported empathy across all participants. Atypical brain function and connectivity in these regions have been previously associated with high levels of CU traits (Finger et al., 2008; Marsh et al., 2008; Marsh, 2018; Waller, Wagner, et al., 2020), CD (Sterzer et al., 2005) and psychopathy (Blair et al., 2014; Cheng et al., 2012; de Vignemont & Singer, 2006; Kiehl et al., 2001; Lockwood et al., 2013; Marsh, 2018; Marsh et al., 2013; Rilling et al., 2007; Sterzer et al., 2005). These regions have also been linked to CE (vmPFC), affective TOM (vmPFC) (Sebastian et al., 2012), AE processes (ACC/MCC) (Bernhardt & Singer, 2012; Bzdok et al., 2012; Lamm et al., 2011) and CE processes (Bray et al., 2022; Bzdok et al., 2012; Molenberghs et al., 2016; Schurz et al., 2014; Van Overwalle & Baetens, 2009). Previous studies investigating the associations between CU traits and brain regions involved in empathy processes have mainly focused on CD populations. Therefore, the relationship between CU traits and ASD remains speculative. However, in ASD patients, functional abnormalities in regions overlapping those that in our sample were related to CU traits have been linked to ASD symptomatology, with dysfunction in the vmPFC linked to self-other distinction processes (Simantov et al., 2021), whereas the ACC and MCC have been linked to affective functioning

(Klöbl et al., 2022) and repetitive behaviors (Thakkar et al., 2008). Furthermore, the ACC/MCC and vmPFC are part of the default mode network (DMN) (Menon & Uddin, 2010) whose integrity has been associated with social cognition (Mars et al., 2012; Meyer et al., 2012; Schilbach et al., 2008), empathy processes (Oliveira-Silva et al., 2023), prosocial personality traits (Coutinho et al., 2013; Sampaio et al., 2014) and CE (Winters et al., 2021). The DMN has consistently been shown to be disrupted in ASD patients (Chen et al., 2016; Glerean et al., 2016; Lynch et al., 2013; Mason et al., 2008; Moseley et al., 2015; Nielsen et al., 2013; Yerys et al., 2015; Ypma et al., 2016). Thus, structural abnormalities in vmPFC and ACC/MCC and associated with CU traits might significantly contribute to symptoms of ASD, impairing social cognition and potentially exacerbating their empathy deficits. Our supplemental analysis revealed structural differences in amygdala, insula and hippocampus in patients with CU trait scores above the clinical cutoff (Docherty et al., 2017) (Supplementary Figure 4, Supplementary Table 8). This is in support of previous findings linking these brain regions to the presence of high CU traits (Ibrahim et al., 2019; Waller, Hawes, et al., 2020). These regions have been either linked to AE or global empathy (Bray et al., 2022; Cardinale et al., 2019; Fan et al., 2011; Goerlich-Dobre et al., 2015; Lozier et al., 2014; Marsh et al., 2013; Stern et al., 2019) and with the amygdala being a hub for overall emotion-related processing (Gothard, 2020; Šimić et al., 2021) it is conceivable that CU traits might also represent a transdiagnostic indicator for emotion processing deficits. The presence of CU traits might therefore play an important role in a range of emotion-related processes such as empathy, with deficits displayed not only in patients with CD but also in other psychiatric disorders (Kraiss et al., 2020; Kret & Ploeger, 2015; McTeague et al., 2020).

In ASD and TD groups, self- and parent-reports showed low correlations in AE and no correlations in CE. Furthermore, no correlations in CE or AE were observed between self- and parent-reports in the CD group implying that these reports could measure different concepts of empathy. Notably, there is still a lack of consensus on the definition of the concept of empathy (Coplan, 2011; de Vignemont & Singer, 2006; Eklund & Meranius, 2021; Engelen & Röttger-Rössler, 2012). This highlights the key role of the questionnaire used, and the potential need to collect both self- and parent-reported measures in young clinical populations with ASD and CD. This study has potential limitations. For the ASD group, only adolescents with high functioning autism or Asperger's syndrome were recruited, to overcome possible language and cognitive barriers (Betancur, 2011) which necessarily limits the generalizability of our findings to a subgroup within this heterogeneous disorder. Previous findings revealed no differences in social skills between ASD youth with and without intellectual disabilities (Baker & Blacher, 2020) however,

whether there are empathy differences needs to be further investigated. Furthermore, although we included female and male participants in our study, the large majority of participants in both patient groups are males. While potentially reflecting the higher prevalence rate among males in both disorders (Loomes et al., 2017; Merikangas et al., 2010), sex differences have been described in both disorders (Fairchild et al., 2013; Ibrahim et al., 2021; Lai & Szatmari, 2020; Napolitano et al., 2022; Ypma et al., 2016). Our supplementary results are also indicative of a potential impact of sex on self-reported AE, however, given the low numbers of females in the patient groups, results remain preliminary. Hence, future studies should explore potential sex-specific differences in empathy capacities in samples with a more balanced female-to-male ratio. An additional aspect to consider is the presence of comorbidities, especially Attention Deficit Hyperactivity Disorder (ADHD), a common comorbid diagnosis in ASD and CD youth (Antshel & Russo, 2019; Fairchild et al., 2019). The presence of both ADHD and CU traits in neurodevelopmental disorders is common (Squillaci & Benoit, 2021). Although CU traits have been discussed as a cross-disorder indicator for empathy deficits, these might also overlap with empathy deficits described in ADHD (Braaten & Rosén, 2000; Maoz et al., 2019; Parke et al., 2021). Thus, investigating the potential influence of both CU traits and ADHD symptomatology in these disorders might help to dissect disorder-specific empathy deficits associated with CU traits and/or ADHD. Finally, larger sample sizes would be needed. Model comparison results show low standard errors implying that larger sample sizes are needed to confidently confirm a potentially better model fit with CU traits included in the model.

To sum up, our results do not support the presence of a double dissociation in AE and CE deficits in youths with ASD or CD. However, CE deficits in CD adolescents were closely related to the presence of CU traits whereas in youths with ASD this association was only observed for AE deficits. Our findings however, confirm the association between CU traits and global empathy deficits (Jones et al., 2010; Waller et al., 2015). This also highlights CU traits as being a potentially transdiagnostic indicator for empathy and possibly overall emotion processing deficits, which extends previous findings linking symptomatic overlaps between ASD and CD youth with CU traits (Carter Leno et al., 2015; Frick et al., 2013; Herpers et al., 2016; Kaat & Lecavalier, 2013; Pasalich et al., 2014). The lack of a significant association between CU traits and CE deficits in the ASD group might be suggestive of disorder-specific empathy deficits going beyond the influence of CU traits. Thus, specific CE deficits might represent a core impairment in ASD which could be specifically targeted by interventions to improve empathy skills in this disorder. Given the discrepancy in the measures of empathy, future studies might consider the combination of self-and

parent-reports and task-based empathy measures to detect specific AE/CE deficits associated with ASD and CD psychopathologies.

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## *4. Study 3: Linking heart rate variability to psychological health and brain structure in adolescents with and without conduct disorder*

Authors: Ana Cubillo[1,2]†, Antonia Tkalcec[1*]†, Helena Oldenhof[3], Eva Unternaehrer[1], Nora Raschle[4], Gregor Kohls[5], Lucres Nauta-Jansen[6], Amaia Hervas[7], Aranzazu Fernandez-Rivas[8], Kerstin Konrad[9], Arne Popma[10], Christine Freitag[11], Stephane de Brito[12], Graeme Fairchild[13], Christina Stadler[1]

[1]Department of Child and Adolescent Psychiatry (research section) University Psychiatric Clinics, Basel, Switzerland

[2]Zurich Center for Neuroeconomics, Department of Economics, University of Zurich, Zurich, Switzerland

[3]Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Child and Adolescent Psychiatry, Amsterdam Public Health, Amsterdam, the Netherlands

[4]Jacobs Center for Productive Youth Development, University of Zurich, Zurich, Switzerland

[5] Department of Child and Adolescent Psychiatry, Faculty of Medicine, TU Dresden, Dresden, Germany

[6] Child and Adolescent Psychiatry Amsterdam UMC, Amsterdam, The Netherlands

[7] Hospital Universitario Mutua Terrassa, IGAIN, Barcelona, Spain

[8] Biocruces Bizkaia Health Research Institute, Basurto University Hospital, University of the Basque Country, Bilbao, Spain

[9] RWTH Aachen University & JARA-Brain Institute, Aachen, Germany

[10] Child and Adolescent Psychiatry Amsterdam University Medical Centers, Amsterdam, The Netherlands

[11] Child and Adolescent Psychiatry, Goethe University, Frankfurt, Germany

[12] University of Birmingham, Birmingham, United Kingdom

[13] Developmental Psychopathology, University of Bath, Bath, United Kingdom

†These authors contributed equally to this work and share first authorship

**Abstract**

**Aims:** Heart rate variability (HRV) measures have been suggested in healthy individuals as a potential index of self-regulation skills, which include both cognitive and emotion regulation aspects. Studies in patients with a range of psychiatric disorders have however mostly focused on the potential association between abnormally low HRV at rest and specifically emotion regulation difficulties. Emotion regulation deficits have been reported in patients with Conduct Disorder (CD) however, the association between these emotion regulation deficits and HRV measures has yet to be fully understood. This study investigates (i) the specificity of the association between HRV and emotion regulation skills in adolescents with and without CD; and (ii) the association between HRV and grey matter brain volumes in key areas of the central autonomic network which are involved in self-regulation processes, such as insula, lateral/medial prefrontal cortices or amygdala.
**Methods:** Respiratory sinus arrhythmia (RSA) measures of HRV were collected from adolescents aged between 9-18 years (693 CD (427F)/753 typically developing youth (TD) (500F)), as part of a European multi-site project (FemNAT-CD). The Inverse Efficiency Score, a speed-accuracy trade-off measure, was calculated to assess emotion and cognitive regulation abilities during an Emotional Go/NoGo task. The association between RSA and task performance was tested using multilevel regression models. T1-weighted structural MRI data were included for a subset of 577 participants (257 CD (125F); 320 TD (186F)). The CerebroMatic toolbox was used to create customised Tissue Probability Maps and DARTEL templates, and CAT12 to segment brain images, followed by a 2x2 (sex x group) full factorial ANOVA with RSA as regressor of interest.
**Results:** There were no significant associations between RSA and task performance, neither during emotion regulation nor during cognitive regulation trials. RSA was however positively correlated with regional grey matter volume in the left insula ($p$ FWE=0.011) across all subjects.
**Conclusions:** RSA was related to increased grey matter volume in the left insula across all subjects. Our results thus suggest that low RSA at rest might be a contributing or predisposing factor for potential self-regulation difficulties. Given the insula's role in both emotional and cognitive regulation processes, these brain structural differences might impact either of those.

## 1. Introduction

Heart Rate Variability (HRV) is a psychophysiological measure that captures beat-to beat vagal modulation of the heart rate. It has a relatively stable, trait-like character and has consistently been associated with physical and psychological wellbeing (Balzarotti et al., 2017; B. L. Henry et al., 2010; Kemp & Quintana, 2013; Kim et al., 2018; Perna et al., 2020; Thayer et al., 2010, 2012). Autonomic system adjustment to contextual demands is regulated by the Central Autonomic Network (CAN), a brain network which receives input from both the sympathetic and parasympathetic branches of the Autonomic Nervous System (ANS) underlying not only the control of autonomic responses but also visceromotor, neuroendocrine and behavioural responses (Appelhans & Luecken, 2006b; Benarroch, 1993; Thayer et al., 2009b, 2012; Valenza et al., 2019; Verberne & Owens, 1998). Key components of the CAN include the anterior cingulate, insula, orbitofrontal and ventromedial prefrontal cortices, together with amygdala, thalamus, subthalamic and brain stem nuclei (Benarroch, 1993; Valenza et al., 2019; Verberne & Owens, 1998). These structures are not only involved in autonomic regulation but also in the implementation of emotional and cognitive self-regulation processes (Beauchaine & Thayer, 2015b; Thayer et al., 2009b; Thayer & Lane, 2000, 2007b; Thayer & Siegle, 2002b; Thayer & Sternberg, 2006). Furthermore, the Neurovisceral Integration Model postulates HRV as an index of functional integrity of brain structures involved in higher executive functions including working memory, inhibitory control as well as in emotion regulation (Thayer et al., 2009b; Thayer & Lane, 2007b). Measures of vagal function such as HRV, primarily mediated by parasympathetic vagal innervation, can also index inhibitory prefrontal processes involved in stress response, being therefore indicative of the ability of the autonomic system to respond and flexibly adjust to contextual demands (Appelhans & Luecken, 2006b; Thayer et al., 2012).

Individuals with low HRV show heightened reactivity to emotional stimuli (Balzarotti et al., 2017) as well as difficulties in emotion regulation and impulse control in daily life (D. P. Williams et al., 2015). In line with this, recent evidence from meta-analytic studies has shown that low HRV measures are observed across several different psychiatric disorders (Heiss et al., 2021; Kim et al., 2018; Koch et al., 2019; Schneider & Schwerdtfeger, 2020), including Conduct Disorder (CD) (de Looff et al., 2022), hence suggestive of its potential transdiagnostic character. Low HRV has been associated with antisocial and aggressive behaviours (Portnoy & Farrington, 2015b), callous-unemotional traits (Duindam et al., 2021), depressive symptoms or suicidal ideation (Gentzler et al., 2012; Koenig et al., 2016; Rottenberg, 2007; Wielgus et al., 2016) or anxiety disorders (Chalmers et al., 2014), thus supporting the idea of HRV as a potential index of deficits

in emotion regulation processes and psychological well-being (Thayer et al., 2012). ANS indicators have indeed long been discussed as potential biomarkers for CD (Fairchild et al., 2019b), a highly impairing psychiatric disorder emerging in childhood or adolescence characterized by severe antisocial and aggressive behaviour. However, evidence from a recent review and meta-analyses (de Looff et al., 2022; Fanti, 2018b) have suggested a high physiological heterogeneity, where the association between ANS function and CD or antisocial behaviours might vary as a function of the clinical subtype, as well as of the ANS measures and analytical methods used. How ANS function might impact the phenotypic presentation of CD is thus not yet fully understood.

At the neural level, individual differences in HRV measures at rest have shown a positive association with cortical thickness in the dorsal anterior cingulate gyrus in healthy young adults (Winkelmann et al., 2017) as well as in war veterans (Woodward, 2008). However, in healthy adults also negative associations were found between HRV and grey matter volumes in subcortical and limbic regions including the putamen, caudate, amygdala, insula or superior temporal gyrus (Wei et al., 2018) while others found no association (Kumral et al., 2019). HRV measures have been shown to be highly sensitive, influenced by a number of factors such as sex, age, SES or variations in the assessment methods used (Shaffer & Ginsberg, 2017). Thus, the mechanism underlying the association between brain structures and HRV measures in healthy populations remains unclear.

Patients with a diagnosis of CD have been reported to have abnormal structure and function in regions including the insula, amygdala, temporal cortex and ventral striatum (Alegria et al., 2016; Fairchild et al., 2019b; Noordermeer et al., 2016; Raschle et al., 2015, 2019; J. C. Rogers & De Brito, 2016). This association has been frequently discussed in the context of emotion regulation deficits (R. J. R. Blair et al., 2014b, 2018; Burke et al., 2010; Frick & Viding, 2009; Raschle et al., 2019). However, children and youths diagnosed with CD show highly heterogeneous symptomatic (Fairchild et al., 2019b), neurocognitive (Kohls, Fairchild, et al., 2020a), and physiological profiles (de Looff et al., 2022). The Research Domain Criteria (RDoC) (Insel et al., 2010) adopts a dimensional approach in which specific alterations in predefined biological systems lead to various symptomatic presentation. The RDoC approach could therefore contribute to improve the understanding of the high heterogeneity present in neuropsychiatric disorders, as in CD. Thus, psychophysiological measures have been suggested as having the potential to help disentangle the heterogeneity within CD populations. Given the association between HRV and emotion regulation deficits, HRV has been discussed as a potential physiological marker for CD. However, recent studies using different HRV indices such as Respiratory Sinus Arrythmia (RSA) or Pre-ejection

Period (PeP) did not find significant associations between ANS activity and CD (Oldenhof et al., 2019) or antisocial behaviours considered from a dimensional perspective (Prätzlich et al., 2019). While different psychophysiological measures can be closely interrelated, subtle differences between groups with small effect sizes might be overlooked depending on the measure selected. Furthermore, the association between HRV and emotion regulation in patients with CD might differ significantly based on symptomatic presentations or comorbidities (Fanti, 2018b; Fanti et al., 2019). Thus, altered HRV has been shown in patients with CD and comorbid internalizing disorders, but not in those with callous-unemotional traits (Fanti, 2018b). In addition, different factors such as Body-Mass Index (BMI), socio-economic status (SES), medication intake, sports (Oldenhof et al., 2019; Prätzlich et al., 2019), the type of task and analyses used or the physiological outcome investigated (de Looff et al., 2022) might influence HRV measures hence contributing to the heterogeneous body of evidence.

Most of the research studies on the role of HRV in patients with CD have focused on its potential association with emotion regulation deficits (Fanti, 2018b). However, HRV might be associated with more generic self-regulation skills (Holzman & Bridgett, 2017b; Zahn et al., 2016). Successful self-regulation skills are crucial for goal-directed behaviour and require the implementation of selective and sustained attention, cognitive control and inhibition of inadequate emotional and behavioural responses (Robson et al., 2020b). Consequently, successful self-regulation skills require the ability to regulate both emotional and cognitive processes. The available evidence seems to suggest that HRV could indeed be better understood as a general index of regulatory processes, as it has been shown to be associated with top-down self-regulation abilities (Holzman & Bridgett, 2017b), executive function (P. G. Williams et al., 2019) and performance during inhibition or switch tasks (Zahn et al., 2016). However, the effect might be rather small and moderated by a number of variables, some inherent to the individuals such as age or sex, others related to the metrics used or the methodological approaches followed during the assessments (Zahn et al., 2016).

In summary, the evidence on the association between HRV and emotion regulation capacities in the few existing studies in patients with CD is not consistent (de Looff et al., 2022). Thus, the present study investigates whether HRV might be associated with more generic self-regulation deficits and with individual differences in key components of the CAN, and whether these associations differ between healthy youths and youths with CD. To test this, we capitalized on data collected as part of a European multicenter study (FemNAT-CD Project), which combines psychophysiological (with HRV operationalized via RSA), neuropsychological (performance of an

Emotional Go/NoGo task) and brain structure data in a group of male and female adolescents with CD, as well as of typically developing adolescents. This allowed us to investigate whether there are group differences between adolescents with CD and healthy peers in a) the association between RSA and emotion regulation and cognitive regulation performance during an Emotional Go/NoGo task and b) the potential association between the HRV measures and grey matter volumes in those regions typically defined as part of the CAN (Benarroch, 1993). Based on the available evidence on factors that might potentially influence the association between CD and HRV, we took those variables into consideration including comorbid internalising symptoms or CU traits within the CD group (Fanti, 2018b), as well as age, sex, SES, BMI, cigarette consumption, involvement in sport or IQ (Koenig, 2020; Oldenhof et al., 2019). We hypothesized that if RSA can be considered as a potential general index of self-regulation, we will find that: 1) there will be a positive association between task performance in both the emotional and cognitive regulation conditions of the Emotional Go/NoGo task and RSA measures across all participants, without significant group differences between patients and controls; 2) RSA measures will be positively associated with cortical grey matter volumes in brain regions that are part of the CAN network across all participants, without significant group differences between patients and controls

## 2. Materials and methods

### 2.1 Participants

Participants of this study were part of the *Neurobiology and Treatment of Adolescent Female Conduct Disorder* (FemNAT-CD) project (https://www.femnat-cd.eu), a large European multicenter study investigating gender differences in the neurobiology underlying CD. The final sample (*N*=1446) of this study included 693 CD (427 females) and 753 TD (500 females) youth aged 9 to 18 years (M= 14.36; SD= 2.44 years) who had valid psychophysiological and neuropsychological data. In addition, structural MRI data was available for a subset of participants (N = 577, CD: *n*=257, 125 females; TD: *n*=320, 186 females). Further details regarding the sample characteristics are reported in Table 1.

Participants were recruited using flyers and advertisement in clinics, youth welfare centers, internet forums and schools, in Birmingham and Southampton (UK), Bilbao and Barcelona (Spain), Amsterdam (Netherlands), Aachen and Frankfurt (Germany), Szeged (Hungary), Athens (Greece) and Basel (Switzerland) between 2003 and 2013. CD youth had to fulfil DSM-5 diagnostic criteria for CD (American Psychiatric Association, 2013), while TD youth were included if they did not meet criteria for any current psychiatric disorder and had no previous DSM-IV diagnosis of CD,

ODD or ADHD. Additional exclusion criteria for both groups were a diagnosis of autism spectrum disorder or schizophrenia (ICD-10, DSM-IV-TR or DSM-5), current bipolar disorder or mania, monogenetic disorder, genetic syndrome, any chronic or acute neurological disorder, treatment for epilepsy, history of traumatic brain injury, or IQ < 70. The FemNAT-CD project was conducted in accordance with the Declaration of Helsinki and approved by the European Commission and local ethics committees of all participating sites. All participants and their caregivers provided written informed assent/consent.

### 2.2 Clinical and behavioural measures

*Clinical Interviews and Questionnaires*

Participants and their parents/caregivers were assessed via a semi-structured interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version, K-SADS-PL) (Kaufman et al., 1997b). In addition, participants and parents/caregivers completed different questionnaires and behavioural measures (for more information please see (Kohls, Fairchild, et al., 2020b)).

Internalising symptoms were assessed through the parent report version Child Behavior Checklist (CBCL) (Achenbach & Rescorla, 2001) and CU traits through the total score from the parent report version of the Inventory of Callous-Unemotional Traits (ICU) (Frick, 2017b). Presence of ADHD was assessed during the interview and coded as a binary variable with 0 and 1 indicating the absence/presence of a current diagnosis of ADHD. We additionally accounted for factors with known impact on HRV measures. These included SES, BMI, number of cigarettes smoked per day and physical activity (hours/week) habits, and intake of medication that might affect parasympathetic nervous system (PNS) function (see Table 1). SES scores were computed using principal component extraction based on parental income, education and occupation (ISCO-08) (*ISCO - International Standard Classification of Occupations*, n.d.) (ISCED) (*International Standard Classification of Education (ISCED)*, 2017), and standardized within each country to avoid potential economic variation at the country level. Current medication intake of compounds that might affect PNS function was assessed by asking the participant, caretaker, therapist, or parent, and coded as a dichotomous variable (yes/no). Depending on age and language, IQ was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI-II) (Wechsler, 1999), the Wechsler Intelligence Scale for Children (WISC) (Wechsler, 2003) or the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 2008) (further details on the assessments and scoring procedures can be found in (Oldenhof et al., 2019) and (Kohls, Fairchild, et al., 2020b)).

Participants performed the emotional Go/NoGo task and underwent a psychophysiological assessment in separate study sessions.

*Emotional Go/NoGo task*

Performance in the Emotional Go/NoGo task was used to investigate the potential specificity of the association between RSA and self-regulation within the emotional or cognitive domains. This is an adapted version of the Emotional Go/NoGo task developed by Hare and colleagues (Hare et al., 2008; Tottenham et al., 2011), where on each trial participants are presented with human faces, which might depict a neutral, happy or fearful expression. Trials are presented in blocks of 48, with only two types of emotions presented on each block. Participants are instructed to press a button as fast as possible when they see one of these expressions (Go trials, 73% trials in each block) and refrain from responding when presented with the second emotional expression of the block (NoGo trials, 27% trials in each block). Stimuli duration was 0.5 s, with a fixed 1s interstimulus interval (for further details, see 67). The different combinations of Go/NoGo trials allows the classification of the blocks as indexing emotion regulation (emotional faces as NoGo stimuli in the context of neutral faces as Go-stimuli) or cognitive regulation (neutral faces as NoGo stimuli in the context of emotional faces as Go-stimuli) (Tottenham et al., 2011). The main performance measures in the task were response times to Go trials and proportion of correct response to NoGo trials. These were first z-transformed and then combined in a single measure to account for the speed-accuracy trade-off that is commonly observed in the task, with slower response in the Go trials being accompanied typically with a higher proportion of successful NoGo trials (Tottenham et al., 2011). Thus, the Inverse Efficiency Scores (IES) (Townsend & Ashby, 1983) were calculated indicating the ratio of z-transformed mean reaction time (Go trials) to z-transformed correct responses to NoGo stimuli (1- incorrect responses to NoGo trials) (Tottenham et al., 2011).

*Psychophysiological assessment*

The procedures followed to acquire and process the electrocardiogram and respiratory rate (RR) data have been described in detail elsewhere (Oldenhof et al., 2019). In short, to ensure familiarization with the setting and minimize potential effects of stress, application of H98SG ECG Micropore electrodes was followed by a 10-minute habituation period. Next, a 5-min excerpt from an aquatic video (Coral Sea Dreaming, Small World Music Inc.) was presented on a DELL Latitude E5550 Laptop with Sennheiser HD 201 earphones, to obtain a baseline measure for HRV. Prior to the assessment, participants were asked to refrain from smoking (1h), and from consuming alcohol

or drugs (24h) (A detailed description of the psychophysiological measurement procedure can be found in (Oldenhof et al., 2019; Prätzlich et al., 2019)).

Heart and respiration rate (RR) were assessed to compute RSA. RSA is a common measure for heart-rate variability (HRV) as it indexes parasympathetic activity, which a growing body of research suggests to be linked with emotion regulation capacities (Beauchaine & Bell, 2020). Respiration cycle and ECG were recorded using a VU-AMS device (Vrije Universiteit Ambulatory Monitoring System) (E. de Geus et al., 2015). Raw data was pre-processed using automated and manual steps provided by the VU-DAMS software package version 3.9 to ensure high data quality. RSA was subject to natural-log transformation prior to the analyses to approach a normal distribution of the data (Beauchaine et al., 2019).

### 2.3 MRI acquisition

Each site followed a site qualification procedure before starting data collection to ensure comparability of MRI data acquisition. Images were acquired using either a Siemens Trio (Frankfurt and Southampton), Siemens Prisma (Aachen and Basel) or Philips scanner (Birmingham) – all at 3 Tesla. Structural T1-weighted magnetization prepared rapid gradient echo (MPRAGE) images were acquired for each participant which included 192 slices, field of view 256 mm, voxel size 1x1x1 mm, repetition time 1900ms, echo time 2.42 (Aachen and Basel), 2.74 (Frankfurt), 3.7 (Birmingham), or 4.1ms (Southampton), flip angle 9 degrees.

### 2.4 Statistical analysis

*Behavioural analysis.*

All analyses were conducted using R (Version 4.1.2) (Team, 2017) implemented on RStudio (Version 1.4.1717). Missing values on the relevant variables to be included in the models were imputed using the "mice" packed to implement Multiple Imputation by Chained Equations (Buuren & Groothuis-Oudshoorn, 2011). Details on the missing data for each variable are shown in Table 1. All behavioural and clinical variables were z-transformed before being entered in the analyses.

We examined the association between RSA and performance measures in the Emotional Go/NoGo task (IES for emotion regulation and cognitive regulation conditions), with RSA values entered as predictors and task as dependent variables with the main regressors of interest being RSA and group (CD vs TD).

Multilevel mixed models (MLM) were used for all behavioural data analyses, with the data nested by data collection site to account for dependency in observations using the package nlme (Pinheiro et al., 2018) and with maximised log-likelihood ('ML') as estimation method.
Patients with CD often present with comorbid internalising symptoms and CU traits, which have been previously shown to drive psychophysiological heterogeneity (Fanti, 2018b). To further investigate whether including these variables would improve the data fit, we conducted a model comparison between models without (simple) and with (extended) these regressors. Thus, in the simple model we included the following regressors as variables of no interest: age, sex, comorbid ADHD, SES, number of cigarettes smoked per day and IQ and in the extended model we added two additional regressors to account for the presence of internalising symptoms and CU traits to compare their relative fit to the data. The two models were then compared using the anova.lme command from the nlme package (Pinheiro et al., 2020). These analyses allowed us to identify whether there was additional variability in the data explained when adding the internalising symptoms and CU traits in the model.

To test the robustness of the results, we repeated the analyses excluding participants whose prescribed medication might have affected their PNS function and therefore, HRV measures.

*MRI data preprocessing and analyses*

Structural MRI data was analysed using the CAT12 toolbox (Gaser et al., 2022) implemented in SPM12 (*Statistical Parametric Mapping*, 2007) using MATLAB (v2020b). Data was preprocessed using standard CAT12 steps, and only those individuals whose data quality was classified by CAT12 as C or higher were included in the analyses. Customised tissue probability maps (TPM) across all individuals were created using the CerebroMatic toolbox (Wilke et al., 2017) and used to segment individual data into the different tissues (grey/white matter and CSF) and smoothed using a 8 mm Gaussian kernel. Total Intracranial Volumes (TIV) were then calculated for each participant. The smoothed grey matter volumes were included in a 2x2 full factorial ANOVA, with gender and group as factors. Standardized RSA values were included as the main regressor of interest, whereas TIV, Age, IQ and site (one regressor per site, using one-hot encoding) are used as regressors of no interest. Analyses were masked for the cortical and subcortical regions which are involved in both emotional and cognitive self-regulation, as well as those typically included as part of the CAN (Benarroch, 1993). These regions included the amygdala, insular cortex, anterior cingulate cortex and medial prefrontal cortex (Supplementary Figure S1). Results are deemed as

significant at a $p < 0.05$, family-wise error (FWE) correction, using the Threshold-Free Cluster Enhancement technique (TFCE) with 5,000 permutations.

## 3. Results

### 3.1 Behavioural Results

Univariate ANOVA comparisons showed that the group of patients with CD differed from the control participants in several demographic variables including age, IQ, SES, medication intake and number of cigarettes per day or hours of sports per week, as well as in clinical variables including comorbid ADHD, CU traits and internalising symptoms (Table 1). The results of the initial multilevel regression analyses on RSA showed significant main effects of age, cigarette, and medication use (Supplementary Table S1) which we then included in our main analysis as covariates. When Group was included as a regressor in the model (as a factor with two levels: TD and CD), no significant effect of group was observed, suggestive of no RSA differences between the two groups when potential influencing factors (age, medication intake or cigarette consumption) are taken into consideration.

**Table 1. Demographics and clinical characteristics of the participants**

| | **TD (N=753)** | | **CD (N=693)** | | *t-value* | *p-value* |
|---|---|---|---|---|---|---|
| | *Mean (SD)/sum* | *NR missing values* | *Mean (SD)/sum* | *NR missing values* | | |
| Sex | 500F/253M | 0 | 427F/266M | 0 | -1.755 | 0.080 |
| Age (Years) | 14.138 (2.477) | 0 | 14.385 (2.285) | 0 | -3.451 | 0.001 |
| IQ score | 103.695 (12.363) | 12 | 94.665 (12.465) | 46 | -5.134 | < 0.001 |
| CU traits | 16.809 (7.594) | 0 | 33.78 (11.867) | 28 | 21.424 | < 0.001 |
| Internalising symptoms | 5.772 (5.814) | 125 | 13.68 (9.912) | 212 | 8.742 | < 0.001 |
| ADHD | 0% | 4 | 31.9 % | 6 | 333.2 | < 0.001 |
| PNS medication intake | 3.2 % | 5 | 32.6 % | 8 | 8.542 | < 0.001 |

| | | | | | | |
|---|---|---|---|---|---|---|
| BMI | 20.743 (4.179) | 72 | 22.158 (4.578) | 93 | 1.737 | 0.083 |
| SES | 0.345 (0.91) | 28 | -0.412 (0.949) | 88 | -6.133 | < 0.001 |
| Cigarettes per day | 0 (2) | 49 | 5 (7) | 53 | 7.872 | < 0.001 |
| Sports (h) /week | 4.663 (4.637) | 121 | 3.72 (4.357) | 116 | -2.656 | 0.008 |

The table shows the mean and standard deviation for each group as well as the group differences for the key demographic variables and symptomatic scores utilized in the present study. For each variable and within each group, the number of participants with missing value for the corresponding value is shown. Missing values were imputed using the MICE package in R with 5000 imputations using all of the available data for those participants used in the present study. Between group comparisons in the key variables shown in the table were conducted after imputation, and they do not differ from those before the imputation. CD = Conduct Disorder group, TD = Typically Developing Adolescents, CU traits= Callous Unemotional Traits total score of the ICU questionnaire, Internalising symptoms = Total score on internalising symptoms subscale of the parent reported CBCL questionnaire, ADHD = ADHD criteria fulfilment according to the DSM-5 coded as a binary variable with 1/0 indicating the fulfillment/not fulfillment of criteria for a diagnosis of ADHD at the time of the interview, IQ = Intelligence quotient (total score of the WASI, WISC or WAIS), PNS medication intake = indicates the number of individuals with a positive intake of medication affecting Parasympathetic Nervous System (PNS) activity at the time of the assessment, BMI = Body-Mass-Index, SES = Socio- economic status based on parental income, education and occupation. Significant group difference = $p < 0.05$. Except for sex and BMI, all other variables significantly differed between groups.

*Emotional Go/NoGo task performance*

For IES, significant group differences between CD patients and controls were observed during both task trial conditions, with the CD group showing a lower speed-accuracy trade-off than their healthy counterparts ($p<0.001$; Table 2). However, we did not find an association between RSA and IES (Table 3) in either task trial condition, and excluding participants taking medication with potential PNS effects did not alter these results (Table 4).

To further investigate the role of internalising symptoms and CU traits in the association between RSA and emotion and cognitive regulation measures, we conducted post-hoc exploratory analyses including total subscale scores for internalising symptoms (CBCL) and total sum scores

for CU traits (ICU) in the extended model (Table 5). We found no significant association between RSA and IES, and model comparison results suggested no significantly better model fit for the extended model (Table 6).

**Table 2. Group differences in task performance and RSA**

| | **TD (N=753)** | **CD (N=693)** | *t-value* | *p-value* |
|---|---|---|---|---|
| | *Mean (SD)* | *Mean (SD)* | | |
| RSA | 1.881 (0.237) | 1.847 (0.246) | -0.645 | 0.519 |
| IES Cognitive Regulation | 0.049 (4.169) | -0.023 (3.511) | 4.535 | < 0.001 |
| IES Emotion Regulation | 0.137 (3.279) | 0.112 (3.531) | 3.921 | < 0.001 |

Outcome of the regression models to investigate group differences between adolescent with CD diagnosis compared to TDs in the main variables of interest: RSA and the Inverse Efficiency Scores (IES) as a Speed-Accuracy trade off score of z-transformed mean reaction time (Go trials) and z-transformed correct response rate to NoGo trials (1-incorrect response rate to NoGo trials) in the emotion regulation and cognitive regulation conditions of the task. RSA results were computed using a multilevel model analysis including the following variable of interest: group, and the following variables of no interest which, based on our results in Supplementary Table 1 show an influence on RSA. These variables were age, medication intake and cigarettes smoked per day. IES results were computed using a t-test. Significance level = $p < 0.05$. Results for RSA show that when including variables shown to influence RSA, no significant group differences were found. For IES, significant group differences were found in both task trial conditions, emotion and cognitive regulation. During both task trial conditions, the TD group shows higher task performance than the CD group.

**Table 3. Results of multi-level regression analyses on task performance measures**

| IES Cognitive Control | | | | | |
|---|---|---|---|---|---|
| | *Value* | *Std.Error* | *DF* | *t-value* | *p-value* |
| RSA | 0.083 | 0.104 | 1427.000 | 0.799 | 0.425 |
| Group | -0.074 | 0.133 | 1427.000 | -0.554 | 0.580 |

| | | | | | |
|---|---|---|---|---|---|
| Age | 0.093 | 0.112 | 1427.000 | 0.830 | 0.407 |
| Interaction RSAxGroup | 0.018 | 0.102 | 1427.000 | 0.179 | 0.858 |
| IES Emotion Control | | | | | |
| | *Value* | *Std.Error* | *DF* | *t-value* | *p-value* |
| RSA | 0.093 | 0.091 | 1427.000 | 1.020 | 0.308 |
| Group | 0.129 | 0.117 | 1427.000 | 1.105 | 0.269 |
| Age | 0.020 | 0.098 | 1427.000 | 0.200 | 0.842 |
| Interaction RSAxGroup | 0.093 | 0.090 | 1427.000 | 1.037 | 0.300 |

The table shows the results of a multilevel regression analyses to investigate the association between RSA measures and performance measures in the Emotional Go/NoGo task. Key task performance measures were Inverse Efficiency Scores (IES) as a speed-accuracy trade off score of z-transformed mean reaction time (Go trials) and z-transformed correct response rate to NoGo trials (1-incorrect response rate to NoGo trials) in the emotion regulation and cognitive regulation conditions of the task. The multilevel models included additional fixed effects to control covariates for ADHD diagnosis, age, IQ, SES, sex, number of cigarettes smoked per day and as random effect site. All questionnaire scores were t-scored and centered and all variables included in the model were z-transformed. RSA = Respiratory Sinus Arrhythmia measure at baseline, Group = difference between patient group CD and control group TD (reference group = TD), Std. Error = Standard Error, DF = degrees of freedom. Significance level = $p < 0.05$. No significant associations were found between RSA or RSA x Group interactions and task performance measures.

**Table 4. Results of multi-level regression analyses on task performance measures after exclusion of participants with positive intake of medication with potential impact on PNS function**

| IES Cognitive Control | | | | | |
|---|---|---|---|---|---|
| | *Value* | *Std.Error* | *DF* | *t-value* | *p-value* |
| RSA | 0.070 | 0.115 | 1177.000 | 0.604 | 0.546 |
| Group | -0.103 | 0.146 | 1177.000 | -0.703 | 0.483 |
| Age | 0.094 | 0.120 | 1177.000 | 0.783 | 0.434 |
| Interaction RSAxGroup | 0.004 | 0.115 | 1177.000 | 0.035 | 0.972 |
| IES Emotion Control | | | | | |
| | *Value* | *Std.Error* | *DF* | *t-value* | *p-value* |
| RSA | 0.129 | 0.103 | 1177.000 | 1.251 | 0.211 |
| Group | 0.164 | 0.131 | 1177.000 | 1.256 | 0.210 |
| Age | -0.034 | 0.108 | 1177.000 | -0.312 | 0.755 |
| Interaction RSAxGroup | 0.152 | 0.104 | 1177.000 | 1.470 | 0.142 |

The table shows the relationship between RSA and the different dependent variables in the study. Key task performance measures were Inverse Efficiency Scores (IES) as a speed-accuracy trade off score of z-transformed mean reaction time (Go trials) and z-transformed correct response rate to NoGo trials (1-incorrect response rate to NoGo trials) in the emotion regulation and cognitive regulation conditions of the task. Participants were excluded if a psychotropic medication is currently used. Medication intake was coded as a dichotomous variable (0 = no medication and 1 = medication intake). Models included additional fixed effects to control covariates for ADHD diagnosis, age, IQ, SES, sex, number of cigarettes smoked per day and as random effect site. All questionnaire scores were t-scored and centered, and all variables included in the model were z-transformed. RSA = Respiratory Sinus Arrhythmia measure at baseline, Group = difference between patient group CD and control group TD (reference group = TD), Std. Error = Standard Error, DF = degrees of freedom. Significance level = $p < 0.05$. No significant associations were found between RSA or RSA x Group interactions and task performance measures.

**Table 5. Results of multi-level regression analyses on task performance measures including internalising symptoms and CU traits in the model**

| IES Cognitive Control | | | | | |
|---|---|---|---|---|---|
| | *Value* | *Std.Error* | *DF* | *t-value* | *p-value* |
| RSA | 0.083 | 0.103 | 1425.000 | 0.804 | 0.422 |
| Group | -0.232 | 0.159 | 1425.000 | -1.458 | 0.145 |
| Age | 0.081 | 0.112 | 1425.000 | 0.722 | 0.471 |
| Interaction RSAxGroup | 0.023 | 0.102 | 1425.000 | 0.225 | 0.822 |
| IES Emotion Control | | | | | |
| | *Value* | *Std.Error* | *DF* | *t-value* | *p-value* |
| RSA | 0.092 | 0.091 | 1425.000 | 1.016 | 0.310 |
| Group | 0.084 | 0.139 | 1425.000 | 0.603 | 0.546 |
| Age | 0.015 | 0.098 | 1425.000 | 0.150 | 0.881 |
| Interaction RSAxGroup | 0.094 | 0.090 | 1425.000 | 1.044 | 0.297 |

The table shows the relationship between RSA and the different dependent variables in the study including internalising symptoms and CU traits in the model. Key task performance measures were Inverse Efficiency Scores (IES) as a speed-accuracy trade off score of z-transformed mean reaction time (Go trials) and z-transformed correct response rate to NoGo trials (1-incorrect response rate to NoGo trials) in the emotion regulation and cognitive regulation conditions of the task. Models included additional fixed effects to control covariates for ADHD diagnosis, age, IQ, SES, sex, number of cigarettes smoked per day, internalising symptoms, CU traits and as a random effect site. RSA = Respiratory Sinus Arrhythmia measure at baseline, Std. Error = Standard Error, DF =

degrees of freedom. Internalising symptoms = total score of the internalising subscale of the parent reported version of the Child Behavior Checklist (CBCL), CU traits = Total score of the parent reported version of the Inventory of Callous Unemotional traits (ICU). All questionnaire scores were t-scored and centered, and all variables included in the model were z-transformed. Significance level = $p < 0.05$. No significant associations were found between RSA or RSA x Group interactions and task performance measures.

**Table 6. ANOVA model comparison: with and without including internalising symptoms and CU traits in the model**

| IES Cognitive Control | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *Model* | *df* | *AIC* | *BIC* | *logLik* | *Test* | *L.Ratio* | *p-value* |
| Simple model | 1.000 | 12.000 | 8029.777 | 8093.095 | -4002.888 | | | |
| Extended model | 2.000 | 14.000 | 8028.026 | 8101.898 | -4000.013 | 1 vs 2 | 5.751 | 0.056 |
| IES Emotion Control | | | | | | | | |
| | *Model* | *df* | *AIC* | *BIC* | *logLik* | *Test* | *L.Ratio* | *p-value* |
| Simple model | 1.000 | 12.000 | 7659.742 | 7723.061 | -3817.871 | | | |
| Extended model | 2.000 | 14.000 | 7662.819 | 7736.691 | -3817.410 | 1 vs 2 | 0.923 | 0.630 |

The table show the results of the ANOVA model comparison with and without including internalising symptoms and CU traits in the model. The dependent variables are the Inverse Efficiency Scores (IES) as a speed-accuracy trade off score of z-transformed mean reaction time (Go trials) and z-transformed correct response rate to NoGo trials (1-incorrect response rate to NoGo trials) in the emotion regulation and cognitive regulation conditions of the task. The simple model included fixed effects of RSA, ADHD diagnosis, age, IQ, SES, sex and number of cigarettes smoked per day. The extended model included the same fixed effects as in the simple model with additional fixed effects of internalising symptoms and CU traits. The random effect in all models was the data collection site. Model = number of models included for the model comparison, df = degrees of freedom, AIC = Akaike information criterion, BIC = Bayesian information criterion, logLik = log-likelihood, Test = indicating which models are being compared, L.Ratio = Likelihood-ratio test, internalising symptoms = total score of the internalising subscale of the parent reported version of the Child Behaviour Checklist (CBCL), CU traits = Total score of the parent reported version of the Inventory of Callous Unemotional traits (ICU). All questionnaire scores were t-scored and centered, and all variables were z-transformed. Significance level = $p < 0.05$. For IES in both task trial conditions, the extended model did not significantly improve fit to the data.

### 3.2 Structural imaging results

Full factorial analyses showed a significant association between grey matter volume in the left insula and RSA values across all participants (figure 1, red cluster, *pFWE* = 0.011, MNI coordinates: -34; 4; 13, 3416 $mm^3$). There were no significant group, sex or RSA x group interaction effects. To test whether these results would remain significant when only those individuals with higher image quality were included, the analysis was repeated with those participants with image quality B or higher. Results remained essentially unchanged (figure 1, green cluster, *pFWE*=0.034, MNI coordinates: -34, 2, 15; 2597 $mm^3$).

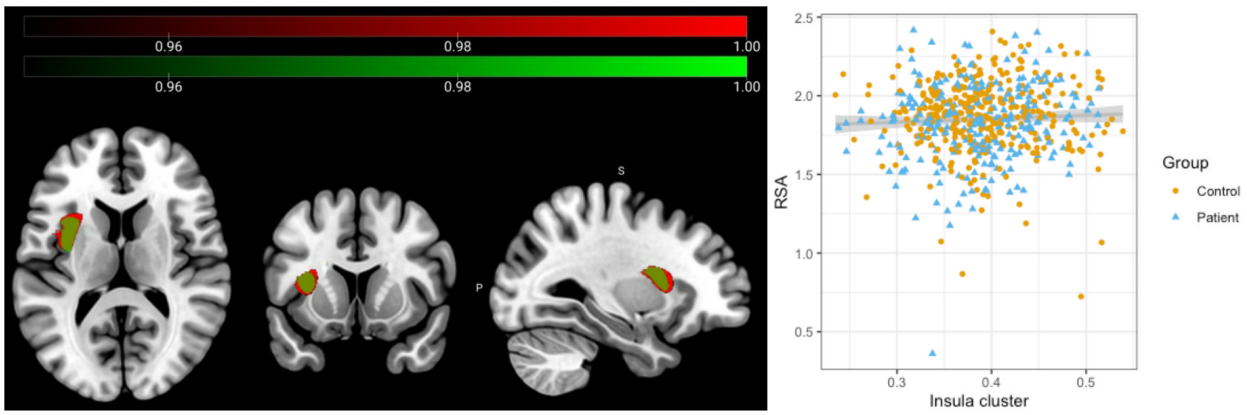


**Figure 1.** Association between Respiratory Sinus Arrhythmia and Insular grey matter volume across all participants. Results of the full factorial analyses with standardized RSA values included as the main regressor of interest and total intracranial volume (TIV), age, IQ and site as regressors of no interest. A significant positive association was observed across all participants between grey matter volume in the left insula and RSA values (Red cluster, N= 577, MNI coordinates: -34; 4; 13; 3417 $mm^3$, *pFWE* = 0.011). Repeating the analysis only including those participants with higher image quality did not change the results significantly (Green cluster, N = 462, MNI coordinates: -34, 2, 15; 2597 $mm^3$, *pFWE* = 0.034).

## 4. Discussion

The current study investigated the association between RSA (as indicator of heart rate variability) and neuropsychological measures of emotion and cognitive regulation in a sample of adolescents with and without a diagnosis of CD. Our results show that RSA was positively associated with grey matter volume in the left insular cortex across all participants, but there were no significant differences between healthy adolescents and those with diagnosis of CD in the strength of the association. However, RSA was not associated with task performance in either cognitive or emotion regulation trials.

Across all participants, individual differences in the specified measure for HRV, RSA, were positively associated with the left insula, key region for emotion and cognitive regulation. Activation in the anterior insula has been associated with sympathetic and parasympathetic activation across a variety of tasks including cognitive, affective and somato-sensory tasks (Beissner et al., 2013), linked to increased autonomic arousal during task performance, and suggested as a potential major site for visceral representations (Critchley et al., 2011). Our results are thus also in line with previous suggestions linking structural and functional abnormalities in the insula with psychopathology (Downar et al., 2016; Ferraro et al., 2022; Goodkind et al., 2015) also showing deficits in the affective and cognitive dimensions of executive function (Namkung et al., 2017).

While the available evidence seems to suggest that right-lateralized neural inputs might be more relevant than their contra-lateral homologous regions for HRV regulation (Beissner et al., 2013; Wei et al., 2018; Winkelmann et al., 2017) our results show an association across all participants with the left anterior insular cortex volume. This brain region has been implicated in both emotion (Uddin et al., 2017) and cognitive regulation processes (Molnar-Szakacs & Uddin, 2022). As part of the salience network, the insula mediates interactions between other large-scale networks such as the default mode network and central executive network (Menon & D'Esposito, 2022). Thus, difficulties in switching between neural circuits in response to environmental demands, also linked with low HRV (Thayer & Brosschot, 2005; Thayer & Lane, 2000) may indicate a vulnerability to generic self-regulation deficits. However, no significant differences between groups were observed. Thus, the observed association between brain structure and HRV might constitute a vulnerability factor for difficulties in self-regulation, contributing to their subsequent manifestation.

Previous studies have found significant negative associations between insular volumes or thickness and HRV measures in healthy adults (Wei et al., 2018). In addition, a recent meta-analyses has shown a significant positive association between cortical thickness and HRV measures in a number of regions including lateral orbitofrontal cortex and insular cortex, declining with age (Koenig et al., 2021). However, in this study data of adolescents and young adults (18-year-olds) were analysed together under the assumption of linear association and therefore any potential quadratic trajectories in this association (potentially showing an inverted-U shape) might have been missed. We however, observed a significant positive association, potentially related to neurodevelopmental processes that are still undergoing during adolescence (Giedd et al., 1999; Shaw et al., 2008). Given the role of the ANS system in supporting the development of the

prefrontal cortex (Koenig, 2020), further studies will be needed to elucidate the longitudinal differences with increasing age. The protracted maturational processes of crucial prefrontal regions for emotion and cognitive regulation including insular cortex increase the likelihood of difficulties that might contribute to the psychopathology (Beauchaine & Cicchetti, 2019). The insular body has indeed shown a quadratic developmental trajectory, with increasing cortical thickness during the first two decades of life and decreasing thereafter (Shaw et al., 2008), a trajectory that mirrors the one described for HRV measures (Koenig, 2020; Silvetti et al., 2001). On older individuals, associations with cortical thickness on lateral OFC and ACC might be more evident (Koenig et al., 2021; Winkelmann et al., 2017; Yoo et al., 2018). Other studies on the other hand have found no associations between HRV and cortical volumes in healthy adult samples but links with functional connectivity instead (Kumral et al., 2019). This might be relevant given the prominent connectivity patterns described between the anterior and middle insula regions and dorsal anterior cingulate cortex (Deen et al., 2011).

While our results suggest no significant association between HRV and different behavioural measures of self-regulation, it might potentially be subject to several individually varying factors such as sex or age or to differences in the sensitivity of different HRV measures (Zahn et al., 2016). In addition, although RSA is commonly used to quantify HRV, there is some debate about its sensitivity, whether correction for heart rate or respiration is necessary (E. J. C. de Geus et al., 2019), with other measures of HRV as potential alternatives (Shaffer & Ginsberg, 2017). Furthermore, there is some evidence from adolescents with self-injury behaviours where it has been shown no association between baseline or reactivity of HRV measures was shown, but only on recovery processes, indicative of a poor ability to regulate response to stressors (Wielgus et al., 2016), or an association between HRV recovery but not at baseline with specific cognitive functions (Kimhy et al., 2013), a lack of association between inhibitory scores and basal HRV measures but with reactivity during inhibitory performance in preschool-aged children with early adverse experiences (Skowron et al., 2014), or differentiated associations as a function of psychopathological profiles (Deutz et al., 2019). One significant limitation is that our psychophysiological measures of HRV were only acquired at rest. Future studies should ideally combine measures of cardiovagal function at rest with the investigation of phasic changes in HRV within the same individuals, including both reactivity (response during stressors or challenging situations) and recovery (function after stressors) capacities (Balzarotti et al., 2017), as well as potentially changes in reactivity over time (Hinnant et al., 2018). This would possibly provide a more complete picture of the association between HRV and self-regulation behaviours.

According to de Looff et al. (22), psychophysiological effects are also dependent on the experimental task, parameters, and analyses. In addition, while the Emotional Go/NoGo task has been shown to measure both emotion and cognitive regulation (Kohls, Baumann, et al., 2020; Tottenham et al., 2011), the "baseline" condition for the cognitive control condition are emotional facial expressions, therefore requiring the processing of facial emotions. The lack of differences between CD youth and healthy controls in the Emotional Go/NoGo task might be due to the inclusion of emotional faces in both emotional and cognitive regulation task conditions, which might interfere with the elicitation of these regulatory processes distinctively enough. To further investigate the specificity of the association between HRV and emotion regulation, future studies using cognitive control tasks not involving facial emotion processing would be needed.

The results of the extended model after inclusion of internalising problems and CU traits scores suggest that the clinical and symptomatologic heterogeneity of the group of CD participants might have significantly contributed to the difficulty to identify potential group differences in the task. This is in line with previous studies suggesting psychophysiological heterogeneity within patients with antisocial and aggressive behaviours (22,31). Thus, potential differences between patients and their healthy counterparts might be easier to identify when such symptomatic differentiations within patients is taken into consideration.

In conclusion, we found a positive association between RSA and gray matter volumes in the left anterior insula. This region has been shown to be involved in emotion and cognitive regulation processes, suggesting that HRV is not solely linked with emotion regulation capacities but more with generic self-regulation processes. Since structural and functional abnormalities of the insula have been linked to many mental disorders including CD, the observed association between brain structure and HRV might constitute one risk factor that, in combination with others, might lead to self-regulation difficulties. As the insula also mediates the switching among different neural circuits in response to environmental demands (Molnar-Szakacs & Uddin, 2022) these processes might be affected in the case of low RSA and associated smaller grey matter volumes. Thus, further research should focus on network dysfunctions rather than individual brain regions, the additional use of HRV reactivity and recovery measures in combination with other ANS indices and the use of paradigms measuring clearly differentiated self-regulation aspects. This might then contribute to provide a clearer picture of the neural mechanisms underlying the association between individual differences in HRV and self-regulation deficits.

**5. Acknowledgements**

We thank all members of the FemNAT-CD consortium for their contributions to the project. We would also like to thank all adolescents, families, institutions and professionals who participated in the study.

**6. Funding**

This study was supported by the European Commission under the 7th Framework Programme [FemNAT-CD, coordinator Christine M. Freitag; grant agreement number 602407]. AT was supported by the Swiss National Science Foundation (Grant no. 100014_185408/1).

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# *5. Discussion*

The studies of this project have investigated if and how potentially transdiagnostic factors detectable early in life, such as atypical eye gaze behavior or co-occurring CU traits, influence different emotion processing deficits described in youth with CD and youth with ASD. Additionally, in CD, emotion, and self-regulation deficits and their psychophysiological correlates are explored. For all three studies, the second focus lies on the neural underpinnings of these emotion processes.

## 5.1 Summary of the findings

**Study 1** aimed to investigate reduced eye gaze as transdiagnostic indicator for facial emotion processing in youth with CD and those with ASD. Behavioral findings show that neither the ASD nor CD group displayed reduced eye gaze compared with the TD group. However, in an extended model, high CU traits have shown a negative interaction effect on eye gaze in the CD group only. These results suggest that eye gaze may not be transdiagnostic but rather disorder-specific, or even specific to a phenotype in CD. At the neural level, gaze behavior was linked to higher brain activation in the insula in ASD compared with CD when angry facial expressions were presented. This suggests that gaze behavior may partially explain the underlying neural mechanisms of facial emotion processing in ASD and CD. The potential transdiagnostic influence of co-occurring CU traits in CD and ASD was investigated in **study 2.** Findings revealed that CU traits impacted empathy deficits in both disorders. However, which aspect of empathy was influenced by CU traits depended on the disorder. Brain structural findings further revealed that CU traits were linked to several regions of the default mode network involved in processes of global empathy and general emotion processing across all participants. Thus, co-occurring CU traits may be linked to neural structures involved in empathy and emotion processes in a transdiagnostic way. Additional analysis on the association between empathy and eye gaze revealed a positive link. Thus, differences in eye gaze might be directly linked to empathy abilities across disorders but the impact of CU traits on this association might be disorder-specific and dependent on the empathy aspect. Brain structural findings in **study 3** showed that HRV was positively linked with brain structural differences in the left anterior insula across all participants suggesting a transdiagnostic association between underlying neural structures of self-regulation and HRV. HRV could, thus, be interpreted as a potential transdiagnostic factor for a higher risk of self-regulation deficits.

### 5.2 Eye gaze as transdiagnostic factor for facial emotion processing deficits

Gaze behavior has shown to be disorder-specific in youth with CD compared with youth with ASD. Results of **study 1** showed that the ASD group did not differ from the TD group in fixations to the eyes but paid more attention to the mouth region than the TD and CD groups. Given that the sample in the ASD group has at least an average Intelligence Quotient (IQ) score (>70), this would be supporting previous findings linking cognitive functioning to higher fixations to the mouth region. According to a recent review and meta-analysis (Riddiford et al., 2022) social functioning is differently linked to eye and mouth gaze. While increased fixations to the eyes have been linked to better social functioning and reduced autism symptom severity, increased fixations to the mouth have been linked to cognitive functioning. In comparison, the presence of CU traits impact eye gaze in youth with CD compared with the TD group confirming previous suggestions of reduced eye gaze being linked to the CU traits phenotype in youth with CD (Carter Leno et al., 2023; Dadds et al., 2014; Demetriou & Fanti, 2022; Muñoz Centifanti et al., 2021). These findings thus, suggest that reduced eye gaze might not be transdiagnostic but instead indicate that atypical gaze patterns, although displayed in different ways, are present in both disorders. This might, however, imply disorder-specific neural underpinnings of facial emotion processing deficits. In line with this thought, differences in brain activation were found between CD and ASD. The ASD group showed higher left anterior insula activation compared with the CD group in response to angry faces, a region involved in multiple emotion processes including self-regulation, empathy and emotional experience among others (Molnar-Szakacs & Uddin, 2022; Uddin et al., 2017). However, controlling for gaze behavior reduced the cluster size. In other words, gaze behavior reduced brain activation differences between ASD and CD implying that gaze behavior may partially account for the functional differences during facial emotion processing in both disorders. Taken together, findings suggest that atypical gaze behavior is found in both disorders. Yet, the nature of the behavioral and underlying neural mechanisms might be disorder specific.

### 5.3 Callous Unemotional traits as transdiagnostic factor for empathy deficits

**Study 2** revealed overlapping empathy deficits in ASD and CD yet controlling for the influence of CU traits showed disorder specificities. In detail, affective empathy deficits in youth with ASD and cognitive empathy deficits in youth with CD have been linked to the presence of CU traits but not cognitive empathy deficits in ASD youth. CU traits might thus, show transdiagnostic characteristics by affecting empathy abilities in both disorders, yet the nature of the influence seems to be specific to the disorder, indicating differences in the cognitive empathy deficits displayed by adolescents

with ASD in comparison to those with CD. In sum, CU traits have consistently shown to drive empathy deficits in youth with CD. In ASD, however, co-occurring CU traits have shown a differential influence on emotion processing deficits. The influence of CU traits in youth with ASD depended on the empathy aspect. This suggests that CU traits have shown transdiagnostic characteristics for empathy deficits, yet the strength of this influence might be dependent on the disorder and, thus, CU traits may impact empathy deficits in youth with ASD and CD in different ways. Structural findings show that, independent of the group, a wide range of brain regions have been linked to CU traits. CU traits were negatively associated with GMV in anterior and mid cingulate, vmPFC, precuneus. This further supports the transdiagnostic impact that co-occurring CU traits might have on processes linked to emotion processing. In sum, CU traits have shown to be associated with emotion processing deficits in a transdiagnostic and disorder-specific way. This implies that CU traits could be seen not only as a subgroup of the CD diagnosis but across disorders and that its transdiagnostic impact at the neural level might be suggestive for an indication of a heightened risk for emotion processing deficits.

### 5.4 The link between eye gaze, empathy abilities and callous unemotional traits

First indications have suggested a potential positive link between empathy and eye gaze (McCrackin & Itier, 2021; Wever et al., 2022). These studies investigated whether empathy abilities and eye gaze behavior are associated with each other in a transdiagnostic way and whether CU traits might also influence this potential link. Additional multilevel analysis confirms a positive link between affective and cognitive empathy and attention to the eye region (tables 1,2 & figure 1).

*Table* 1. Bayes multilevel analysis results of cognitive empathy on fixations to the eyes

| **Fixations to the eyes** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Basic model | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% CI* | *u-95% CI* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | 0.64 | 0.42 | -0.19 | 1.48 | 1 | 1341 | 2151 |
| CD | -0.08 | 0.33 | -0.71 | 0.57 | 1 | 1553 | 2336 |
| Cognitive Empathy | 0.24 | 0.11 | 0.02 | 0.46 | 1 | 1750 | 2694 |
| Extended model | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% CI* | *u-95% CI* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | 0.62 | 0.45 | -0.2 | 1.5 | 1.01 | 572 | 1121 |
| CD | -0.12 | 0.35 | -0.81 | 0.6 | 1 | 555 | 820 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| CU traits | 0.04 | 0.14 | -0.23 | 0.3 | 1.01 | 614 | 1054 |
| Cognitive Empathy | 0.25 | 0.12 | 0.02 | 0.48 | 1 | 761 | 1555 |
| Interaction model | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% CI* | *u-95% CI* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | 0.22 | 0.5 | -0.77 | 1.18 | 1 | 1409 | 2236 |
| CD | -0.44 | 0.44 | -1.31 | 0.41 | 1.01 | 1282 | 2128 |
| CU traits | 0.42 | 0.29 | -0.13 | 1.02 | 1 | 1274 | 2134 |
| Cognitive Empathy | 0.21 | 0.12 | -0.02 | 0.44 | 1 | 1529 | 2792 |
| Interaction ASD x CU traits | -0.43 | 0.35 | -1.14 | 0.25 | 1 | 1359 | 2295 |
| Interaction CD x CU traits | -0.56 | 0.36 | -1.3 | 0.14 | 1 | 1314 | 2447 |

Bayes multilevel regression analyses results of the cognitive empathy scores of the BES on the key dependent variable eye fixations. *Est.Error = estimation standard deviations, l-95% CI = lower credible interval, u-95% CI = upper credible interval, Rhat = convergence of the MCMC algorithm (Gelman and Rubin, 1992), Bulk_ESS = bulk effective sample size estimate, Tail_ESS = tail effective sample size estimate, ASD = youth with autism spectrum disorder, CD = youth with conduct disorder, TD = typically developing youth, BES = Basic Empathy scale*

*Table* 2. Bayes multilevel analysis results of affective empathy on fixations to the eyes

| **Fixations to the eyes** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Basic model | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% CI* | *u-95% CI* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | 0.44 | 0.4 | -0.37 | 1.21 | 1 | 705 | 1464 |
| CD | -0.07 | 0.32 | -0.71 | 0.54 | 1.01 | 735 | 1279 |
| Affective Empathy | 0.24 | 0.11 | 0.03 | 0.45 | 1 | 1073 | 2024 |
| Extended model | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% CI* | *u-95% CI* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | 0.43 | 0.42 | -0.42 | 1.23 | 1 | 456 | 907 |
| CD | -0.1 | 0.35 | -0.78 | 0.58 | 1 | 560 | 850 |
| CU traits | 0.02 | 0.14 | -0.25 | 0.29 | 1.01 | 421 | 779 |
| Affective Empathy | 0.25 | 0.11 | 0.03 | 0.46 | 1.01 | 558 | 979 |
| Interaction model | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% CI* | *u-95% CI* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | 0.1 | 0.48 | -0.83 | 1.04 | 1 | 1316 | 2720 |
| CD | -0.34 | 0.43 | -1.18 | 0.53 | 1 | 1411 | 2353 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| CU traits | 0.37 | 0.28 | -0.18 | 0.94 | 1 | 1427 | 2606 |
| Affective Empathy | 0.23 | 0.11 | 0.01 | 0.44 | 1 | 2000 | 3688 |
| Interaction ASD x CU traits | -0.33 | 0.35 | -1.02 | 0.34 | 1 | 1591 | 2882 |
| Interaction CD x CU traits | -0.59 | 0.35 | -1.29 | 0.08 | 1 | 1417 | 2361 |

Bayes multilevel regression analyses results of affective empathy scores of the BES on the key dependent variable eye fixations. *Est.Error = estimation standard deviations, l-95% CI = lower credible interval, u-95% CI = upper credible interval, Rhat = convergence of the MCMC algorithm (Gelman and Rubin, 1992), Bulk_ESS = bulk effective sample size estimate, Tail_ESS = tail effective sample size estimate, ASD = youth with autism spectrum disorder, CD = youth with conduct disorder, TD = typically developing youth, BES = Basic Empathy scale*

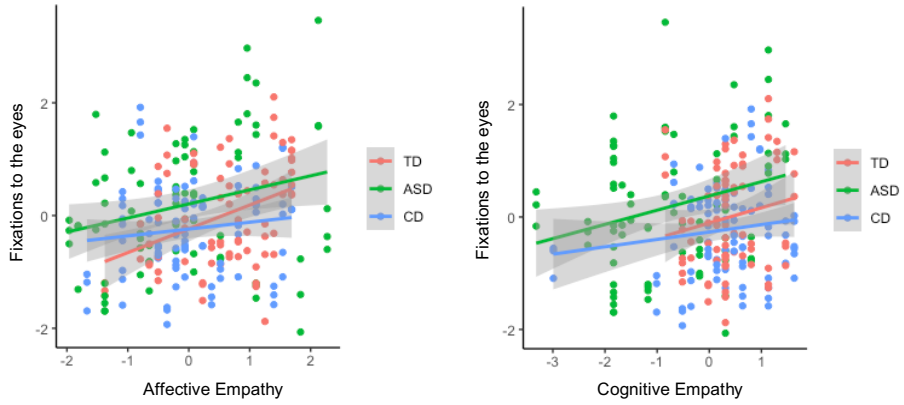


*Figure* 1. This figure shows the correlation analysis results of affective and cognitive empathy scores of the BES and fixations to the eye regions per group across all emotions. *TD = typically developing youth, ASD = youth with autism spectrum disorder, CD = youth with conduct disorder, BES = Basic Empathy scale*

Interestingly, when accounting for the influence of co-occurring CU traits in interaction with the groups, the link between cognitive empathy and eye gaze disappears, while the link between affective empathy and eye gaze remains (tables 1, 2). This, however, raises another question of a transdiagnostic or disorder-specific influence. Results show associations between empathy abilities and eye gaze across all groups suggesting that this association is independent of the group. Given, however, that the results of **study 1** indicate a negative interaction between CD and CU traits on eye gaze behavior and the results of **study 2** suggest that CU traits might drive the cognitive empathy deficits only in CD, there may be a possibility that the influence of CU traits on the link between cognitive empathy and eye gaze is disorder specific. In sum, while CU traits do not impact

the association between affective empathy and eye gaze, CU traits might influence the link between cognitive empathy and eye gaze. While previous findings have specifically linked affective empathy to eye gaze (McCrackin & Itier, 2021; Warnell et al., 2022), the relationship between cognitive empathy and eye gaze is less studied. Nonetheless, an intervention study found that the emotion recognition deficits of fearful faces often in youth with high CU traits is improved by instructions to fixate on the eye region (Muñoz Centifanti et al., 2021). Emotion recognition is described as the first step towards empathic responding, particularly in relation to CU traits (de Wied et al., 2010; Masi et al., 2014; Sharp & Vanwoerden, 2014). Thus, eye gaze may be also a potential treatment target for the improvement of empathy abilities in youth with CU traits. Further studies are thus, needed to explore the potential impact of CU traits on different emotion processes and how they might be linked with each other and for each disorder.

## 5.5 The link between heart rate variability, emotion- and self-regulation

Previous studies have suggested that the phenotypes of CD lie on the opposite spectrum of regulation abilities and HRV. However, the findings of **study 3** did not confirm that co-occurring CU traits or comorbid internalizing problems influence emotion and self-regulation abilities or HRV. This suggests that CU traits do not equal emotion processing deficits in CD youth. This highlights the yet unknown influences of CU traits within CD. However, the results show a positive link between HRV indices and GMV in the left insula in participants with and without CD, a brain region linked to emotion and self-regulation processes (Molnar-Szakacs & Uddin, 2022; Uddin et al., 2017). This would support previous literature suggesting HRV to be a transdiagnostic marker for self-regulation abilities and additionally, a predisposing indicator for potential self-regulation difficulties.

## 5.6 Limitations

### 5.6.1 Small sample sizes

Regarding the findings in **study 1 and study 2,** especially, the brain imaging results need to be interpreted with caution due to small sample sizes. Thus, larger samples are needed to increase the statistical power of the analysis and confidently confirm the results of these studies.

### 5.6.2 Considering CU traits as a multidimensional construct

Based on suggestions made in the previous sections, there are some limitations that need to be considered. To measure the level of CU traits, all studies used the total sum score of a parent reported questionnaire, the Inventory of Callous Unemotional Traits (ICU) (Frick, 2017). The

available evidence, however, suggested that more attention needs to lie on the subscales (Cardinale & Marsh, 2020; Ciucci et al., 2015; Essau et al., 2006; Kimonis et al., 2008; Roose et al., 2010). This would help create a more nuanced distribution of how CU traits might impact individuals across different disorders. Thus, treating CU traits as a construct that is heterogeneous and consists of subdimensions might provide crucial information to understanding emotion processing deficits in individuals with different disorders and co-occurring CU traits. The ICU questionnaire measures CU traits on three subdimensions defined as callousness, unemotional and uncaring scales. Callousness describes having a lack of empathy and guilt over wrongdoings. Uncaring is marked by unconcern about performance or concern for others and unemotionality is shallow affect or emotional reactivity. It is, thus, conceivable that each link and emotion processing impairment of each disorder might be differently driven by these subdimensions. For adults, a recent meta-analysis found that externalizing behavior in psychopathy was more strongly predicted by the callous and uncaring subscale than unemotionality (Cardinale & Marsh, 2020). Unemotionality however, is described as a strong predictor for prosocial emotion deficits and dysfunction displayed by a lack of empathy (Ciucci et al., 2015; Kimonis et al., 2008; Roose et al., 2010), negative affect (Essau et al., 2006) and emotional reactivity to distressing stimuli (Kimonis et al., 2008) and has, thus, been discussed as an independent aspect from the other subdimensions. This has also been supported by neuroimaging findings linking externalizing behaviors to bilateral amygdala gray matter volumes and being driven specifically by callousness (Caldwell et al., 2019) and uncaring scales (Cardinale et al., 2019). Unemotionality however, might be associated with a genetic etiology distinct from the other two subdimensions (Henry et al., 2016).

Taken together, CU traits as a construct may not be homogeneous but instead consist of different distinct yet correlated dimensions. Differences in the level of CU trait subscales found for different individuals might, thus, not only demonstrate the differences in facets of CU traits but also in the way they present themselves in that individual. Thus, apart from using the total sum score of the ICU, additional consideration of the different subscales might help to better understand these different subgroups of individuals having different CU characteristics. In general, differences in emotion processing deficits found in each disorder might be partly linked to the differences found within the CU traits construct and its subdimensions. Comparing these different aspects and subtypes of CU traits within each disorder might help to disentangle why CU traits have differently impacted emotion processing in youth with ASD and youth with CD.

### 5.6.3 Generalizability

Due to the IQ inclusion criteria, our patient samples are homogeneous in their intelligence level and do not represent all patients of a disorder with all its heterogeneity. This limitation also applies for the diagnostic criteria of no comorbid anxiety or depressive disorder which are often diagnosed in ASD and CD (Bougeard et al., 2021; Fairchild et al., 2019; Hossain et al., 2020). Our findings thus, cannot be generalized for a disorder. Another limitation is that other potential transdiagnostic influences have been accounted for but not been further investigated. For instance, high attention deficit hyperactivity disorder (ADHD) comorbidity rates are described in ASD and CD populations and the impact of ADHD symptoms on emotion processing deficits and gaze patterns has been repeatedly found in other studies (Airdrie et al., 2018; Braaten & Rosén, 2000; Maoz et al., 2019; Parke et al., 2021). There is, thus, a possibility that CU traits and ADHD symptomatology show overlaps in their influence on these deficits. This, however, goes beyond the scope of this thesis and thus needs to be investigated in further studies.

## *6. Conclusion*

Eye gaze and CU traits have both been linked to emotion processing deficits and are detectable in CD and ASD populations. This raises questions of potential transdiagnostic impacts of both factors on emotion processing deficits in CD and ASD. However, differences in eye gaze have been mainly observed in those with ASD while high CU traits have been mainly linked with CD.

Although atypical gaze behavior has been shown in CD and ASD, underlying mechanisms might differ depending on the disorder. In ASD, fixating on the mouth region might act as a strategic response to avoid hyperarousal while in those with CD and high CU traits reduced eye gaze might be linked to hypo arousal causing a lack of interest in salient social cues of facial expressions. Thus, considering the influence of gaze behavior could help in identifying disorder specific mechanisms underlying emotion processing impairment.

CU traits have shown both transdiagnostic and disorder-specific influences. The nature of the influence might partially depend on the disorder and the type of emotion processing investigated. Youth with CD and high CU traits show a consistent link with empathy deficits and reduced eye gaze but not youth with ASD. Notably, genetic, and environmental influences linked to CU traits might help in understanding these specificities displayed by the disorders. Structural neuroimaging findings also suggest a transdiagnostic link of CU traits with GMV in brain regions underlying empathy and other emotion processes across all participants. This might indicate that the presence of CU traits represents a heightened risk for brain structural differences underlying

different emotion processes. Thus, independent of the disorder or groups investigated, CU traits have shown a transdiagnostic influence on brain structures underlying emotion processing. How CU traits impact each disorder or group might be more disorder-specific at the behavioral or psychometric level. The way the behavioral and neural levels function together might, thus, be different based on the disorder or group. Additionally, the direct link between empathy abilities and eye gaze confirms previous findings (McCrackin & Itier, 2021; Wever et al., 2022) and suggests that higher eye gaze may be linked to higher empathic abilities, independent of the disorder. CU traits might, however, disrupt this association in a subgroup of individuals of the sample. Nonetheless, there are also first suggestions for eye gaze as a possible treatment target for emotion processing in individuals with CD with high CU traits and ASD (Dadds et al., 2014; Griffin et al., 2021; Muñoz Centifanti et al., 2021). Given that higher fixations to the mouth and higher insula activation in ASD in **study 1** might be due to an avoidance of unpleasant hyperarousal, the question arises whether, in this case, sensitivity to eye gaze shows similar improvement in emotion processing abilities or whether it might aggravate the level of distress experienced by the individual affected. However, since there are only a few studies that have investigated the treatment effects of targeting eye gaze in ASD and CD with high CU traits, the underlying neural mechanisms are not fully understood. Regarding HRV, its association with the anterior insula may suggest that HRV is a potential transdiagnostic indicator for a heightened risk for self-regulation deficits.

The findings of these studies, thus, suggest that CU traits and HRV might play a transdiagnostic role at the neural or physiological level for different emotion subprocesses. This highlights the importance of including neurobiological correlates in future studies to prevent overlooking potential indications for emotion processing deficits. Furthermore, although atypical gaze behavior was shown in CD with high CU traits and ASD, neural findings indicate that brain activation patterns during facial emotion processing might be disorder specific. Yet, gaze behavior has shown to reduce these differences in brain activation patterns. This suggests that gaze behavior may at least partially help to explain facial emotion processing deficits in ASD and CD. Additionally, the link between empathy abilities and eye gaze across all participants has revealed that eye gaze may potentially be a transdiagnostic treatment target for empathy deficits.

## *7. Outlook*

Emotional and social functioning is often impaired and described as fundamental to the development and maintenance of antisocial behaviors (Van Goozen et al., 2007). Yet, these

behaviors manifest in different ways with different etiologies (Hudziak et al., 2007). The implementation of dimensional approaches has helped gain deeper knowledge of antisocial behaviors as well as to develop more tailored treatment options (Cuthbert & Insel, 2013; Hudziak et al., 2007; Skeem et al., 2014; Van Goozen et al., 2007). However, research is lagging in comparison studies between disorders with impairments in similar domains of functioning. Apart from ASD and CD, patients with numerous other disorders are exhibiting impairments in emotion processing. By comparing disorders in these domains, individual emotion processing deficits and underlying neural mechanisms allow researchers to draw conclusions on a specific type of emotion processing dysfunction on the individuals concerned. In turn, shared emotion processing deficits linked to (endo-)phenotypes may help explain the heterogeneity within a disorder. For this, not only the subdimensions in different emotion processes need to be further investigated but also the potentially transdiagnostic factors. For instance, the broad definition of CU traits needs to be further specified to help better understand the differences in emotion processing deficits found in different disorders. Future studies should, thus, investigate the subdimensions of CU traits to close gaps on how differently CU traits might impact and are displayed in individuals with different conditions and disorders. If emotion processing deficits are observed in an individual, the potential presence of (endo-) phenotypes should be considered as it may help explain part of the impairment. Thus, it would be potentially beneficial to target impairments linked to gaze behavior and CU traits for treatments and interventions.

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## *Acknowledgements*

I started my PhD just before the onset of the Covid-19 pandemic, a period with many challenges and uncertainties for the private and professional life. I would like to express my deepest gratitude to the exceptional individuals who supported and guided me and played significant roles in my PhD journey despite the many unforeseen obstacles that arose.

First and foremost, I owe a tremendous debt of gratitude to my supervisors who guided me through my PhD years. Without their invaluable guidance, this project would not have been possible. Professor Christina Stadler gave me the opportunity to work in her team and pursuing the first steps into my research career. She taught me a lot about endurance and staying positive and hopeful during difficult times which is an invaluable asset I will keep and take into my future. Ana Cubillo's interest and knowledge for research has been a true inspiration to me. I was especially grateful for her relentless support, guidance and advice in the last four years. I have been extremely lucky to have a supervisor who cared so much about my work, and who responded to my questions and queries so promptly.

I would also like to thank the research group of Professor Stadler, especially Eva and Donja who always had an open ear when I needed advice or just a cup of coffee and some mental support. I was very lucky to have had such great colleagues which I will miss dearly. A PhD can often feel lonely which is why I also want to thank the master students of my PhD project Maria, Alessandro and Vithusan who helped in the data collection and analysis and made struggling times feel less draining which was a crucial part in getting to the finish line of my PhD.

A big thank you to my family and especially my parents for always supporting me in my academic aims in life. They have inspired me to proceed academia in the first place and have been my steady rock from afar during my studies until this day. Additionally, I am very thankful for Niklas who continuously supported me, sacrificed his time, and always believed in me. Finally, a huge thank you to my dear friends Eva, Stefanie, Viktoria, Delfine and Süheyla. I could always rely on them for emotional support and finding fun and joy during stressful times.

# *Curriculum Vitae*

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**Personal information**

| | |
|---|---|
| Name | Antonia Luise Tkalcec |
| Date of Birth, Town | 26.10.1992, Offenbach a.M. |
| Nationality | British, Croatian |
| Languages | German (Native Speaker), English (Native Speaker), French (B2); Croatian (B2) |

**Education**

| | |
|---|---|
| 10/2002-06/2012 | Leibnizgymnasium, Offenbach am Main, Germany |
| 10/2012 – 07/2013 | Sinology studies, Goethe-University, Frankfurt am Main, Germany |
| 09/2013– 07/2016 | BSc Psychology, Université de Fribourg, Switzerland |
| 09/ 2016 – 01/2019 | MSc Psychology, University of Zürich, Switzerland |
| 09/ 2019 - | PhD in Psychology, University of Basel, Switzerland<br>Research department of Child and Adolescent Psychiatry, Psychiatric University Clinics Basel |

**Practical experience**

| | |
|---|---|
| May - July 2015 | Research internship in the EEG study: “The Neural Correlates of Expectations Effects”. Department of Cognitive Neuroscience, Université de Fribourg, Switzerland |
| May 2016 – June 2017 | Research Assistant in an MRI and EEG study: “Neural Correlates of Traumatic Memory Consolidation and Retrieval”. Department of Biopsychology, University of Zurich, Switzerland |
| 09/2015-06/2016 | Bachelor Thesis: ”A comparison of cortisol and slow wave sleep in |

| | |
|---|---|
| | traumatic memory consolidation” |
| 07 – 09/2017 | Psychology internship at the Zentralinstitut für seelische Gesundheit (ZI) Mannheim, Germany |
| 09/2017-01/2019 | Master Thesis: “Gender role perception, sexual violence and risk behaviour in women from former Burundian rebel groups” |
| 10/2017 – 06/2018 | Psychology internship at the day clinic for addiction treatment Curaneo AG, Zurich, Switzerland |
| 08/2018 – 01/2019 | Research Assistant for Prof. Maercker, Department of Psychopathology and Clinical Intervention, University of Zurich, Switzerland |
| Since 09/ 2019 | Doctoral Research Associate in the Department of Clinical Neurodevelopment, University Psychiatric Clinic Basel, University of Basel, Switzerland |

**Trainings in academia**

| | |
|---|---|
| 12/2019 | MRI safety certificate, Radiology & Nuclear Medicine Clinic, University Hospital Basel |
| 10/2020 | Statistical Parametric Mapping (SPM) course (online) |

**Publications**

**2023** Cubillo, A.*, **Tkalcec, A.***, Oldenhof, H., Unternaehrer, E., Raschle, N., Kohls, G., Nauta-Jansen, L., Hervas, A., Fernandez-Rivas, A., Konrad, K., Popma, A., Freitag, C., De Brito, S., Fairchild, G., & Stadler, C. (2023). Linking heart rate variability to psychological health and brain structure in adolescents with and without conduct disorder. Frontiers in Psychiatry, 14, 1101064. https://doi.org/10.3389/fpsyt.2023.1101064

***Shared first authorship**

**Tkalcec A**.*, Bierlein M.*, Seeger-Schneider G., Walitza S., Jenny B., Menks W. M., Felhbaum L. V., Borbas R., Cole D. M., Raschle N., Herbrecht E., Stadler C.† & Cubillo A.† (2023). Empathy deficits, callous-unemotional traits and structural underpinnings in autism spectrum disorder and conduct disorder youth. Autism Res. Aug 7. doi: 10.1002/aur.2993. Epub ahead of print. PMID: 37548142.

***Shared first authorship**

† Shared last authorship

**Preprints, under review or in press**

**Tkalcec A.,** Baldassarri A., Junghans A., Somasundaram V., Menks W. M., Fehlbaum L. V., Borbàs R., Raschle N., Seeger Schneider G., Jenny B., Walitza s., Cole D. M., Sterzer P., Santini F., Herbrecht E., Cubillo A. † & Stadler C. † (2023). Gaze behavior, facial emotion processing and neural underpinnings: A comparison of adolescents with autism spectrum disorder and conduct disorder.

† Shared last authorship

**Peer-reviewed conference presentations, abstracts and posters**

**2023** Tkalcec, A., Bierlein, M., Seeger-Schneider, G., Walitza, S., Jenny, B.. Menks, W. M., Felhbaum, L., Borbas, R., Raschle, N., Herbrecht, E., Stadler, C. & Cubillo, A. (2023). Disorder-specific deficits in cognitive and affective empathy in autism spectrum disorder and conduct disorder youth: relevance of callous-unemotional traits and structural underpinnings. Poster presented at 20th international congress of ESCAP in Copenhagen, Denmark.

Tkalcec, A., Bierlein, M., Seeger-Schneider, G., Walitza, S., Jenny, B.. Menks, W. M., Felhbaum, L., Borbas, R., Raschle, N., Herbrecht, E., Stadler, C. & Cubillo, A. (2023). Disorder-specific deficits in cognitive and affective empathy in autism spectrum disorder and conduct disorder youth: relevance of callous-unemotional traits and

structural underpinnings. Oral presentation at the 14th WTAS Congress in Freiburg, Germany.

**2022** Tkalcec, A., Cubillo, A., Oldenhof, H., Unternaehrer, E., Raschle, N., Fehlbaum, L., Freitag, F., Popma, P., Nauta, L., Fairchild, F., de Brito, S., & Stadler, C. (2022). Heart rate variability (HRV), self-regulation (SR) and brain structures in adolescents with and without conduct disorder. Poster presented at the FLUX 2022 in Sorbonne, France.

Tkalcec, A., Cubillo, A., Oldenhof, H., Unternaehrer, E., Raschle, N., Fehlbaum, L., Freitag, F., Popma, P., Nauta, L., Fairchild, F., de Brito, S., & Stadler, C. (2022). Heart rate variability (HRV), emotion regulation and brain structures in adolescents with and without conduct disorder. Presentation at the Symposium: Female adolescent conduct disorder: Neurobiological findings and their relation to intervention outcome, 19th international congress of ESCAP in Maastricht, The Netherlands.

Tkalcec, A., Cubillo, A., Oldenhof, H., Unternaehrer, E., Raschle, N., Fehlbaum, L., Freitag, F., Popma, P., Nauta, L., Fairchild, F., de Brito, S., & Stadler, C. (2022). Herzratenvariabilität, Emotionsregulation und Gehirnstrukturen bei Jugendlichen mit und ohne Störungen im Sozialverhalten. Presentation at the Symposium: Neurobiologische Grundlagen zu Störungen des Sozialverhaltens – neueste Ergebnisse der FemNAT-CD-Studie, XXXVII DGKJP Kongress in Magdeburg, Germany.

**2021** Tkalcec, A., Cubillo, A., Oldenhof, H., Unternaehrer, E., Raschle, N., Fehlbaum, L., Freitag, F., Popma, P., Nauta, L., Fairchild, F., de Brito, S., & Stadler, C. (2021). Linking psychological health and autonomic nervous function to adolescents. Poster presented at the SRCD 20201 Biennial Virtual Meeting Conference.

# *Appendices*

## Appendix A: Supplementary Material Study 1

*Supplementary Table 1.* Bayes Multilevel Regression Results for fixation durations

| | Eye Durations | | | | | Mouth Durations | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *Hypothesis* | *Est.* | *SE* | *95% CI* | | *Post. Prob.* | *Est.* | *SE* | *95% CI* | | *Post. Prob.* |
| ASD<TD | -0.28 | 0.43 | -1.01 | 0.42 | 0.74 | 0.84 | 0.43 | 0.12 | 1.56 | 0.03 |
| CD<TD | -0.43 | 0.34 | -0.99 | 0.14 | 0.9 | 0.26 | 0.34 | -0.31 | 0.82 | 0.22 |
| ASD=CD | 0.18 | 0.3 | -0.31 | 0.68 | 0.27 | 0.58 | 0.31 | 0.06 | 1.08 | 0.03 |

This table depicts the bayes multilevel regression analysis results testing the one-sided hypotheses on key dependent variables: Fixation durations on the eyes and mouth regions across all emotions. *Est. = Estimate, SE = Standard-Error, 95% CI = Credible interval, Post. Prob = Posterior Probability under the hypothesis against the hypothesis' alternative. Hypothesis = direction of tested hypothesis, ASD = youth with autism spectrum disorder, CD = youth with conduct disorder, TD = typically developing youth*

*Supplementary Table 2.* F test peak clusters, MNI coordinates and cluster size

| **Emotion Anger** | | | | | |
|---|---|---|---|---|---|
| Size in voxels | Peak | PeakXYZ | Peak Structure | XYZ | Structure |
| 6810 | 1 | 35.6×24.2×-1.7 | Insula (R) | 35.6×17.6×-1.0 | Insula (R), Inferior Orbitofrontal Cortex (R), Putamen (R), Rolandic Cortex (R) |
| 6507 | 1 | -39.6×20.5×-6.9 | Inferior Orbitofrontal Cortex (L) | -34.5×13.1×2.7 | Insula (L), Inferior Orbitofrontal Cortex (L), Putamen (L), Rolandic Cortex (L), Inferior Frontal Gyrus (L) |
| 3020 | 1 | -27.8×-3.8×-19.4 | Hippocampus (L) | -24.9×-2.4×-15.7 | Amygdala (L), Hippocampus (L),Temporal Cortex (L), ParaHippocampus (L), Insula (L) |
| 2199 | 1 | 25.3×-3.8×-15.0 | Amygdala (R) | 26.0×-1.6×-17.9 | Amygdala (R), Hippocampus (R), |

| | | | | | ParaHippocampus (R), Fusiform Gyrus (R) |
|---|---|---|---|---|---|
| 1701 | 1 | -11.6×34.5×-4.7 | | 0.2×44.8×-3.2 | Anterior Cingulate (L,R), Medialorbitofrontal Cortex (R,L), Medialfrontal Cortex (R) |
| 85 | 1 | -29.3×-2.4×-31.9 | ParaHippocampus (L) | -30.0×-3.1×-29.7 | ParaHippocampus (L), Fusiform Gyrus (L), Hippocampus (L) |

**Emotion Fearful**

| Size in voxels | Peak | PeakXYZ | Peak Structure | • XYZ | Structure |
|---|---|---|---|---|---|
| 4314 | 1 | -39.6×20.5×-6.9 | Inferior Orbitofrontal Cortex (L) | -34.5×19.0×0.5 | Insula (L), Inferior Orbitofrontal Cortex (L), Inferior Frontal Gyrus (L), Putamen (L) |
| 3391 | 1 | 35.6×24.2×-1.7 | Insula (R) | 34.9×21.2×-1.0 | Insula (R), Inferior Orbitofrontal Cortex (L), Putamen (R) |
| 2183 | 1 | -5.0×36.0×-7.6 | Anterior Cingulate (L) | -0.5×44.1×-3.9 | Medial Orbitofrontal Cortex (R,L), Anterior Cingulate (L,R), Medialfrontal Cortex (R,L) |
| 389 | 1 | -19.7×-6.0×-12.0 | Hippocampus (L) | -24.1×-3.8×-12.8 | Amygdala (L), Hippocampus (L), Putamen (L) |
| 252 | 1 | -36.7×-6.0×16.0 | Rolandic Cortex (L) | -37.4×-6.0×14.5 | Insula (L), Rolandic Cortex (L) |

**Emotion Neutral**

| Size in voxels | Peak | PeakXYZ | Peak Structure | • XYZ | Structure |
|---|---|---|---|---|---|
| 14096 | 1 | -34.5×22.0×-9.8 | Insula (L) | -33.0×6.5×0.5 | Insula (L), Amygdala (L), Hippocampus (L), Inferior Orbitofrontal Cortex (L), Putamen (L), Rolandic Cortex (L), Inferior Frontal Gyrus (L) |
| 8344 | 1 | 35.6×24.2×-1.7 | Insula (R) | 35.6×19.0×-2.4 | Insula (R), Inferior Orbitofrontal Cortex (R), Putamen (R), Inferior Frontal Gyrus (R) |
| 1200 | 0.9 | 21.6×-3.8×-15.7 | Amygdala (R) | 25.3×-2.4×-17.9 | Amygdala (R), Hippocampus (R), ParaHippocampus (R),Fusiform Gyrus (R), Putamen (R) |

| | | | | | |
|---|---|---|---|---|---|
| 1021 | 0.8 | 41.5×-14.2×6.4 | Insula (R) | 42.2×-12.7×4.2 | Insula (R),Temporal Cortex (R), Heschl's Gyrus (R), Rolandic Cortex (R) |

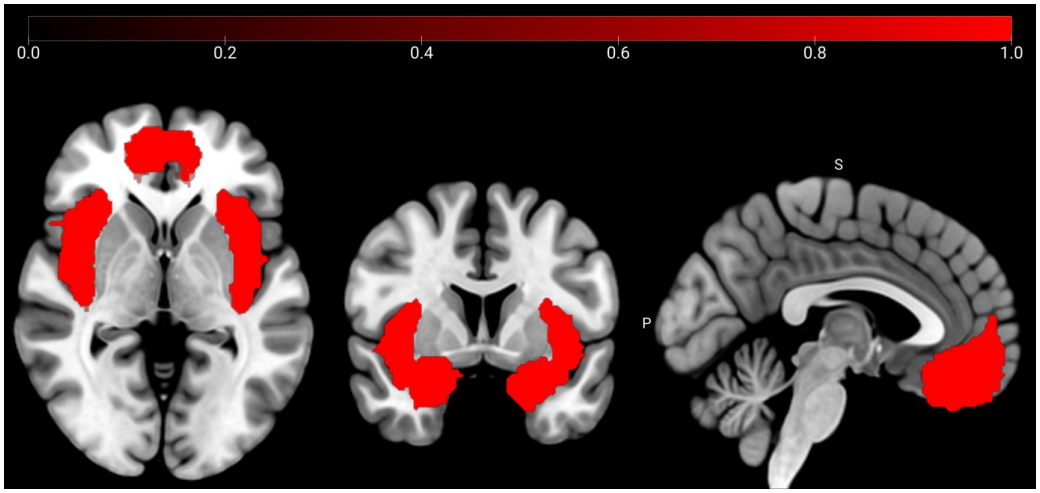
The presented clusters show significant group differences of the F test. Results were estimated using TFCE, FWE-corrected, and thresholded at $p < 0.05$. FWE = Family-wise error correction for multiple comparisons, *TFCE = Threshold Free Cluster Enhancement, MNI =Montreal Neurological Institute, R = Right, L = Left.*

*Supplementary Table 3.* Bayes Regression Results on Insula parameters as outcome variable for the emotion anger

| Model without fixations | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Estimate | Est.Error | l-95% CI | u-95% CI | Rhat | Bulk_ESS | Tail_ESS |
| ASD | 0.5 | 0.28 | -0.06 | 1.05 | 1 | 3590 | 4474 |
| CD | 0.05 | 0.23 | -0.4 | 0.51 | 1 | 3712 | 4865 |
| CU traits | 0.06 | 0.14 | -0.23 | 0.35 | 1 | 3343 | 4115 |
| Sex | -0.09 | 0.14 | -0.35 | 0.17 | 1 | 5633 | 5403 |
| Age | 0.11 | 0.06 | -0.02 | 0.23 | 1 | 7757 | 5401 |
| IQ | -0.04 | 0.07 | -0.18 | 0.1 | 1 | 6925 | 6074 |
| CBCL AP | -0.1 | 0.09 | -0.28 | 0.07 | 1 | 5213 | 5823 |
| Data collection wave | 0.17 | 0.17 | -0.16 | 0.5 | 1 | 5129 | 5299 |
| Interaction ASD x CU traits | -0.03 | 0.19 | -0.41 | 0.35 | 1 | 3931 | 4213 |
| Interaction CD x CU traits | 0 | 0.2 | -0.39 | 0.41 | 1 | 4060 | 5240 |
| Model with fixations to the eyes | | | | | | | |
| | Estimate | Est.Error | l-95% CI | u-95% CI | Rhat | Bulk_ESS | Tail_ESS |
| Fixations to eyes | 0.04 | 0.06 | -0.09 | 0.17 | 1 | 8782 | 6127 |
| ASD | 0.52 | 0.28 | -0.03 | 1.07 | 1 | 3875 | 4837 |
| CD | 0.08 | 0.23 | -0.36 | 0.53 | 1 | 4038 | 5378 |
| CU traits | 0.04 | 0.14 | -0.24 | 0.32 | 1 | 3868 | 4997 |
| Sex | -0.08 | 0.14 | -0.35 | 0.19 | 1 | 6782 | 5724 |
| Age | 0.1 | 0.07 | -0.03 | 0.23 | 1 | 9186 | 5911 |
| IQ | -0.04 | 0.07 | -0.18 | 0.1 | 1 | 8276 | 5765 |
| CBCL AP | -0.1 | 0.09 | -0.28 | 0.07 | 1 | 6048 | 5851 |
| Data collection wave | 0.19 | 0.17 | -0.13 | 0.52 | 1 | 6475 | 5438 |
| Interaction ASD x CU traits | -0.01 | 0.19 | -0.4 | 0.37 | 1 | 4235 | 5438 |
| Interaction CD x CU traits | 0.03 | 0.2 | -0.37 | 0.44 | 1 | 4392 | 5608 |
| Model with fixations to the mouth | | | | | | | |

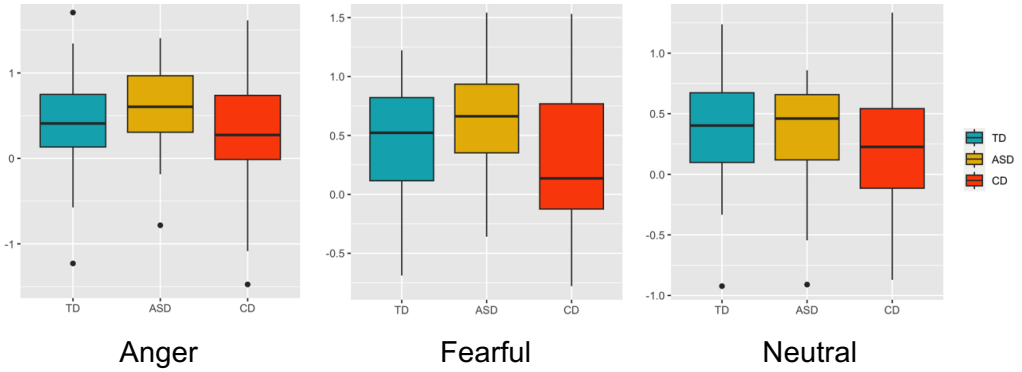
| | Estimate | Est.Error | l-95% CI | u-95% CI | Rhat | Bulk_ESS | Tail_ESS |
|---|---|---|---|---|---|---|---|
| Fixations to mouth | -0.07 | 0.06 | -0.19 | 0.05 | 1 | 9832 | 5462 |
| ASD | 0.56 | 0.28 | 0.01 | 1.12 | 1 | 3682 | 4572 |
| CD | 0.07 | 0.23 | -0.37 | 0.53 | 1 | 4046 | 5357 |
| CU traits | 0.05 | 0.14 | -0.22 | 0.32 | 1 | 4025 | 4750 |
| Sex | -0.06 | 0.14 | -0.33 | 0.21 | 1 | 7780 | 5223 |
| Age | 0.11 | 0.06 | -0.02 | 0.24 | 1 | 10190 | 5907 |
| IQ | -0.04 | 0.07 | -0.18 | 0.1 | 1 | 8371 | 5493 |
| CBCL AP | -0.11 | 0.09 | -0.28 | 0.07 | 1 | 5988 | 5725 |
| Data collection wave | 0.22 | 0.17 | -0.12 | 0.55 | 1 | 6424 | 5975 |
| Interaction ASD x CU traits | -0.02 | 0.19 | -0.39 | 0.36 | 1 | 4363 | 5346 |
| Interaction CD x CU traits | 0.02 | 0.2 | -0.37 | 0.41 | 1 | 4715 | 5129 |

Bayes regression analysis results testing the one-sided hypotheses on key dependent variables: Extracted parameters from the Insula for the emotion anger. Additionally, the number of fixations to the eyes and mouth region were added in separate models as regressors of interest. All included numeric variables were z-scored, the TD group and female sex were set as reference groups. *Est. Error = estimation standard deviations, l-95% CI = lower credible interval, u-95% CI = upper credible interval, Rhat = convergence of the MCMC algorithm (Gelman and Rubin, 1992), Bulk_ESS = bulk effective sample size*
*estimate, Tail_ESS = tail effective sample size estimate, ASD = youth with autism spectrum disorder, CD = youth with conduct disorder, TD = typically developing youth*



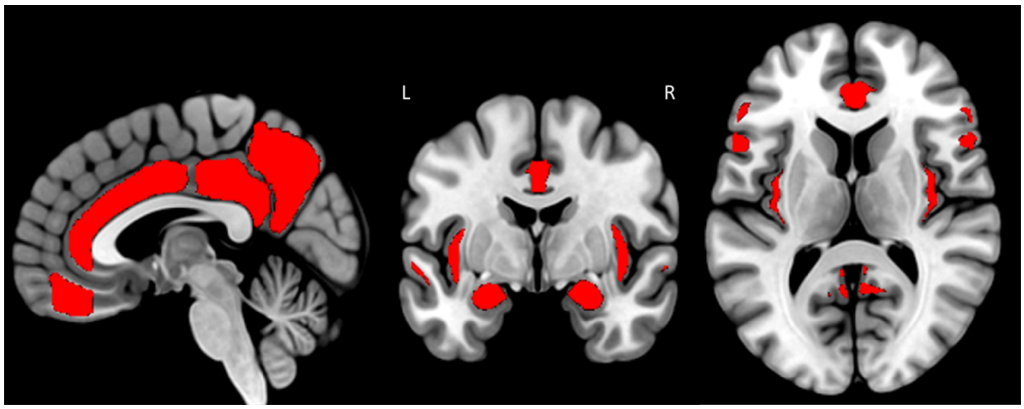

*Supplementary Figure 1.* Combined mask displaying the regions of interest, including areas associated with eye gaze behavior and facial emotion processing (amygdala, insula, ventromedial prefrontal cortex (vmPFC)). The binarized mask was created by combining the

selected regions defined by the Harvard Oxford atlas in FSLeyes (Version 1.3.0) in xjView (Version 10.0), with a threshold set at 50% ROI probability. The image was created via MRIcroGL (Version 1.2.20220720b) (https://www.nitrc.org/projects/mricrogl).

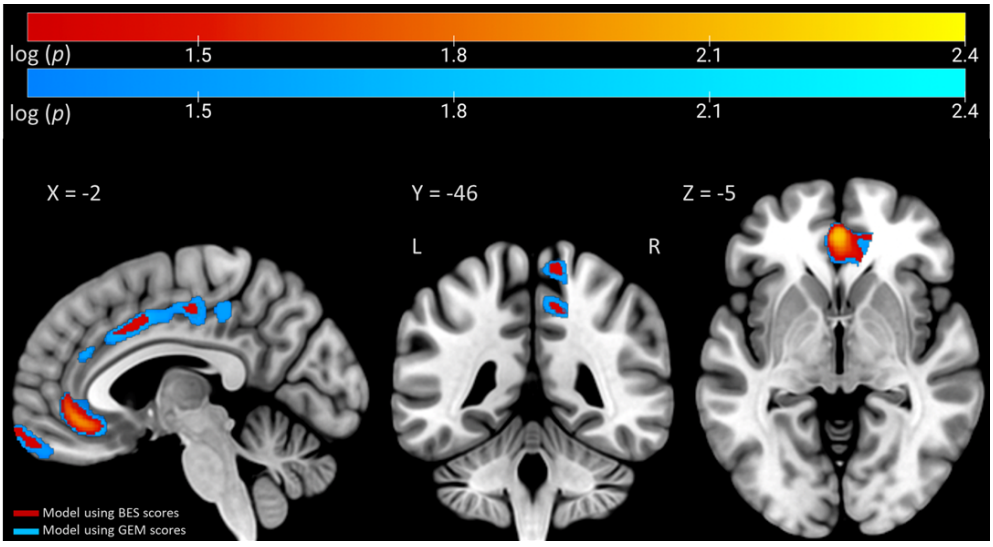



*Supplementary Figure* 2. Boxplots of the extracted insula cluster parameter values (standardized) for each emotion per group. *TD = typically developing youth, CD = youth with conduct disorder, ASD = youth with autism spectrum disorder*

## Appendix B: Supplementary Material Study 2

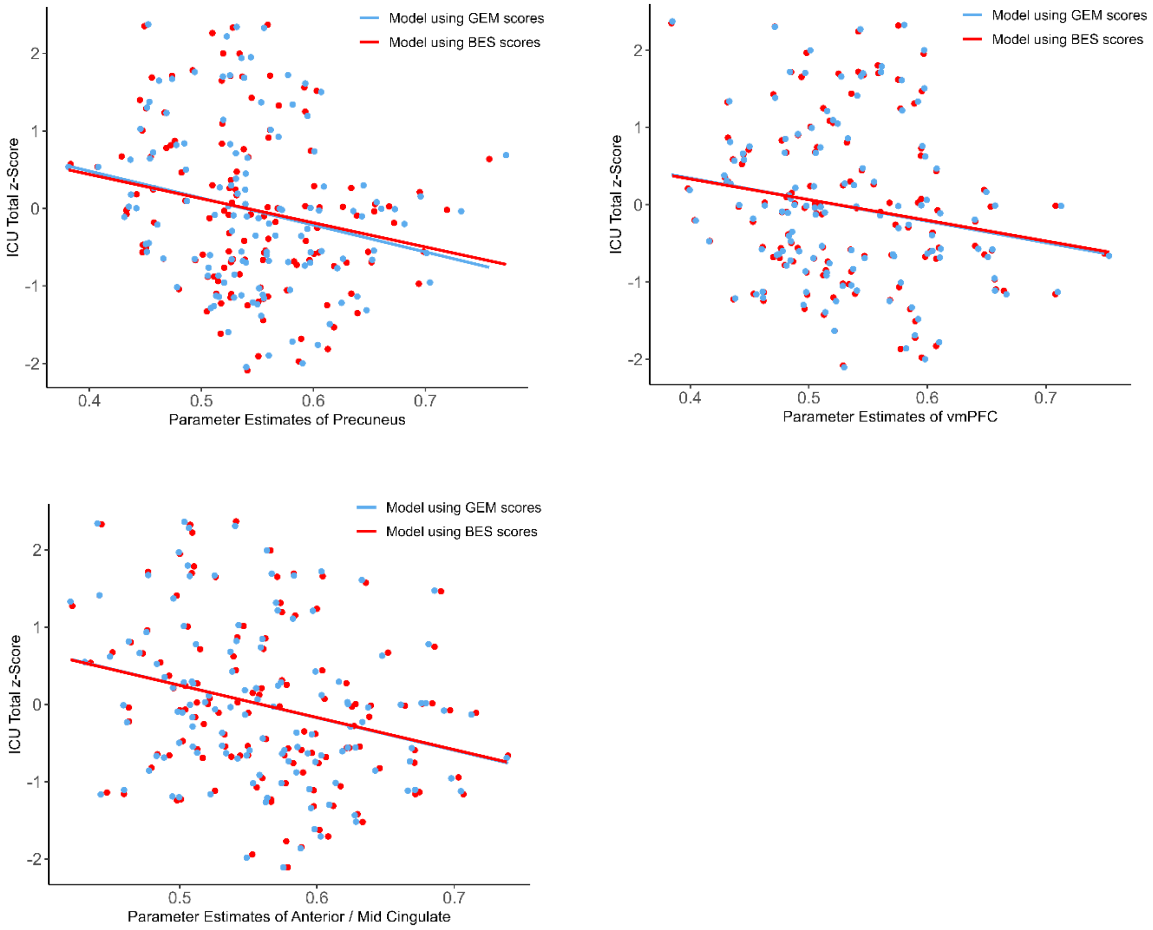



*Supplementary Figure 1. Combined* mask displaying the regions of interest, including areas associated with AE (amygdala, insula, inferior frontal gyrus (IFG), cingulate cortex) and CE (ventromedial prefrontal cortex (vmPFC), temporoparietal junction (TPJ), superior temporal gyrus and precuneus (PCu)). The binarized mask was created by combining the selected regions defined by the Harvard Oxford atlas in FSLeyes (Version 1.3.0) in xjView (Version 10.0), with a threshold set at 50% ROI probability. The image was created via MRIcroGL (Version 1.2.20220720b) (https://www.nitrc.org/projects/mricrogl). *AE = Affective Empathy, CE = Cognitive Empathy.*



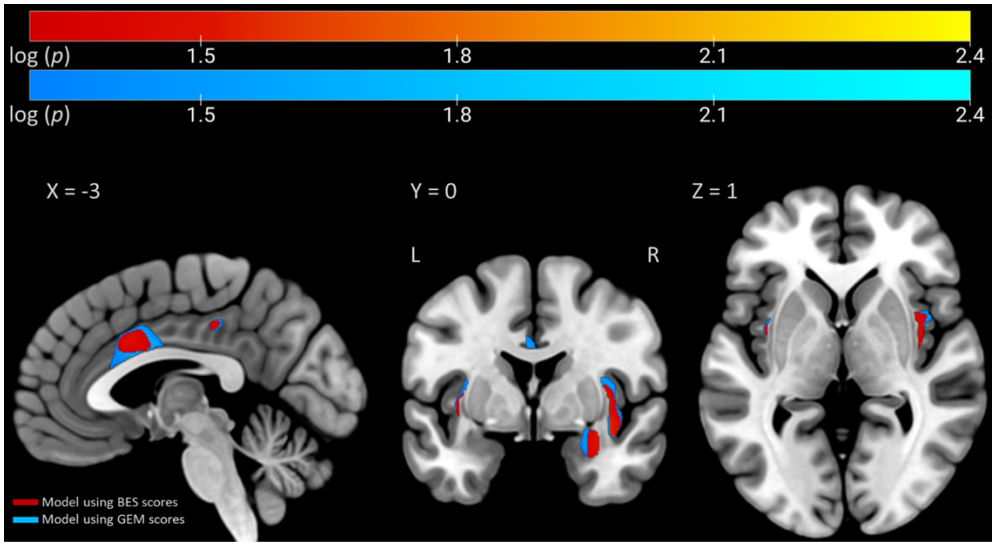

*Supplementary Figure 2.* The overlap of the whole brain full factorial analyses results including AE and CE of either the BES or GEM, CU traits and group as regressors of interest and TIV, age, data collection wave and IQ as regressors of no interest. Green voxels show the overlap between GEM and BES models. Blue voxels show additional negative correlations between

CU traits and GMV associated in the GEM model. Across all participants, significant negative associations were observed between GMV and CU traits in the left ACC and the vmPFC (peak MNI = 3;31;-15, 32457mm3 volume), with all p(FWE) < 0.05. GMV = Gray Matter Volume, CU = Callous-Unemotional traits, BES = Basic Empathy Scale, GEM = Griffith Empathy Measure, AE = Affective Empathy, CE = Cognitive Empathy, TIV = Total Intracranial Volume, IQ = Intelligence Quotient, ACC = Anterior Cingulate Cortex vmPFC = ventromedial Prefrontal Cortex, MNI = Montreal Neurological Institute, FWE = Familywise Error rate



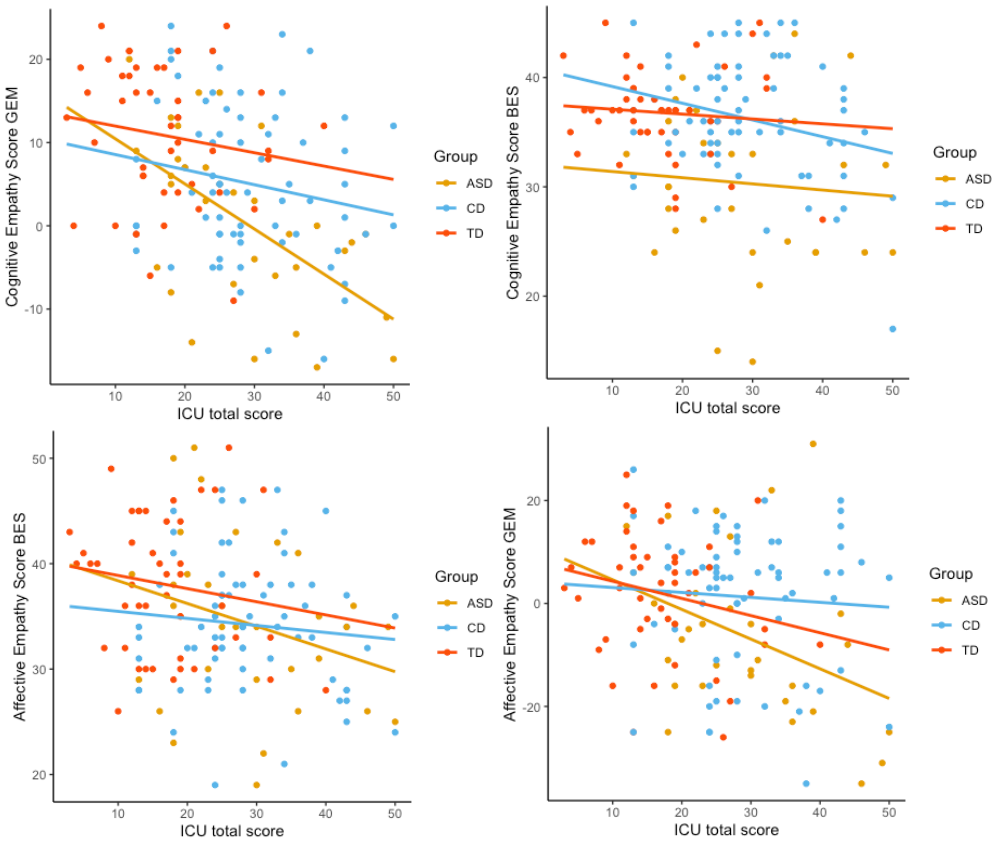

*Supplementary Figure 3.* Negative Correlations Between CU Traits and Parameter Estimates of the ACC/MCC, vmPFC, and PCu by Questionnaire. These three scatterplots display the relationship between z-transformed ICU total scores representing CU traits and parameter estimates of the ACC/MCC, the vmPFC, and the PCu, by questionnaire. Parameter estimates of the ACC/MCC, the vmPFC, and the PCu were extracted via MarsBaR, a toolbox within SPM12, using a combined mask of binarized and 50%-thresholded regions of the Harvard Oxford Atlas in FSL eyes (Version 1.3.0) (https://zenodo.org/record/7038115#.Y9Kly8hKiUc)

together with the respective significant cluster of the SPM analysis (Brett et al., 2002). Note that the results of both models are strongly overlapping, which is why the fit line of the model using GEM scores might be partly covered by the other fit line of the model using BES scores. Negative associations can be found between Cu traits and all displayed regions. CU = Callous-Unemotional traits, ACC = Anterior Cingulate Cortex, MCC = Mid Cingulate Cortex, vmPFC, ventromedial Prefrontal Cortex, PCu = Precuneus, BES = Basic Empathy Scale, GEM =Griffith Empathy Questionnaire, BES = Basic Empathy Scale, GEM = Griffith Empathy Questionnaire, ICU = Inventory of Callous-Unemotional traits.



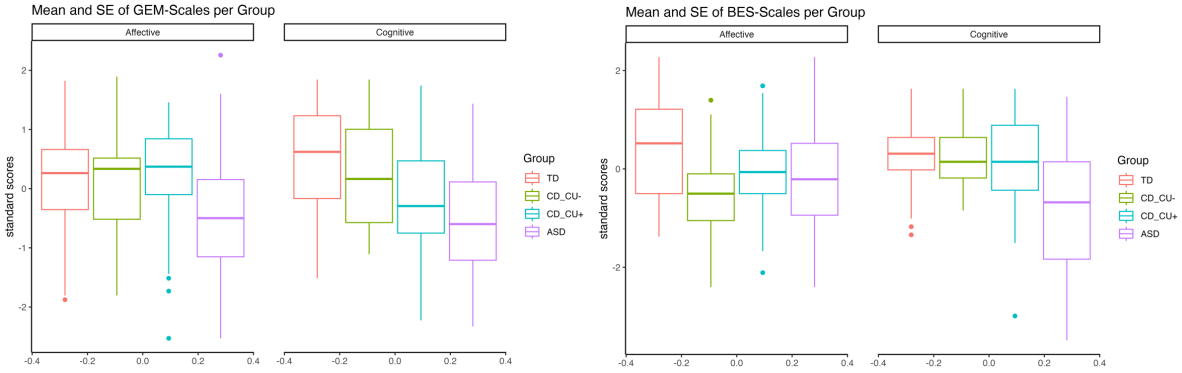

*Supplementary Figure 4*. Region of Interest Analysis of GMV Differences in Subgroups Based on Callous-Unemotional Traits: Clinical Cutoff from Docherty et al. (2017). For comparison to previous work, we conducted a region of interest analysis of GMV to examine structural differences in youths with low versus high levels of CU traits, using the combined mask (see Supplementary Figure 1). To form subgroups of youths with low and high CU traits, we used the clinical cutoff score of 30 as recommended by Docherty et al. (2017) for the parent-rated ICU. Therefore, the patient population was divided into a high (N =36 with CU traits ≥ 30) and a low (N = 49 with CU traits < 30) CU trait subgroup, while the TD group (N = 45) remained the same (Ibrahim et al., 2021). The models were again separated for empathy scores obtained from either the self-reported BES or the other-reported GEM and contained CU subgroups as factor, AE and CE from either the BES or the GEM as regressor, as well as IQ, age, sex, data collection wave, and TIV as covariates. All included variables were z-transformed. Results were estimated using TFCE, FWE-corrected, and thresholded at $p < 0.05$. As part of the TFCE procedure, p-values were log-transformed, with 1.3 representing a p-value < 0.05, and 2

representing a p-value < 0.01 (see CAT12 manual or https://neuro-jena.github.io/cat12-help/). This figure depicts the significant results of the contrast comparing the high CU patient subgroup with the TD group in both models, with red voxels depicting the association in the model using BES scores and blue voxels using GEM scores. In addition to the results of the main analysis investigating the association between CU traits and GMV across all participants, the high CU subgroup within the patient population shows significantly lower GMV in the amygdala, the insula, and the hippocampus when compared to the TD group. The image was created via MRIcroGL (Version 1.2.20220720b) (https://www.nitrc.org/projects/mricrog). *GMV = Gray Matter Volume, CU = Callous Unemotional traits, ICU = Inventory of Callous Unemotional traits, TD = Typically Developing group, BES = Basic Empathy Scale, GEM = Griffith Empathy Questionnaire, AE = Affective Empathy, CE = Cognitive Empathy, IQ = Intelligence Quotient, TIV = Total Intracranial Volume, TFCE = Threshold Free Cluster Enhancement, FWE = Family-Wise Error correction for multiple comparisons, L = Left, R = Right.*




*Supplementary Figure 5*. Self- and parent reported AE and CE subscale scores by CU traits. The scatter plots show the relationships between AE and CE subscale sum scores and ICU total sum scores. Results show a negative correlation among ICU sum scores and AE/CE in both

self-and parent reported questionnaires (BES, GEM). *AE = Affective Empathy, CE = Cognitive Empathy.*




*Supplementary Figure 6*. AE and CE by TD, ASD and CD CU-/+ groups. The boxplots show the z-scored mean sum scores in the self- and parent reported subscales AE and CE among the four groups TD, ASD, CD CU- and CD CU+. Patients in the CD group were split by the median of total sum scores of the Inventory of Callous Unemotional Traits (ICU) (Frick, 2017) (m=25) into those with lower (CD CU-) and higher (CD CU+) scores. *Affective = Affective Empathy, Cognitive = Cognitive Empathy.*

*Supplementary table 1a*. Correlation matrix of self -and parent reports on AE and CE across all participants

| Total sample | | |
|---|---|---|
| | *rho* | *p* |
| Affective Empathy | 0.25 | 0.00 |
| Cognitive Empathy | 0.16 | 0.05 |

This table shows the spearman rank correlation results between self- and parent reported AE and CE subscales across all participants. For the whole sample, significant low positive correlations were found between self- and parent reports in AE. *rho = Spearman's rank correlation coefficient, p = p-value, TD = Typically developing youth, ASD = Patients with autism spectrum disorder, CD = Patients with conduct disorder.*

*Supplementary table 1b*. Correlation matrix of self -and parent reports on AE and CE by group

| | Affective Empathy | | Cognitive Empathy | |
|---|---|---|---|---|
| | *rho* | *p* | *rho* | *p* |
| TD | 0.42 | 0.00 | 0.13 | 0.38 |
| ASD | 0.51 | 0.00 | 0.12 | 0.49 |
| CD | -0.02 | 0.87 | 0.03 | 0.80 |

This table shows the spearman rank correlation results between self- and parent reported AE and CE subscales by group. AE was positively correlated with the TD and ASD group but not the CD group. For CE, no significant correlations were found between self- and parent reports across all groups. *rho = Spearman's rank correlation coefficient, p = p-value, TD = Typically developing youth, ASD = Patients with autism spectrum disorder, CD = Patients with conduct disorder.*

*Supplementary Table 2.* Bayes regression models including the interaction Group x CU traits on self- and parent-reported affective and cognitive empathy

| **Self-report** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Cognitive Empathy | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% CI* | *u-95%* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | -0.83 | 0.27 | -1.37 | -0.32 | 1 | 2163 | 1973 |
| CD | 0.06 | 0.24 | -0.4 | 0.53 | 1 | 1895 | 1854 |
| CU traits | -0.03 | 0.19 | -0.39 | 0.34 | 1 | 1601 | 2100 |
| Interaction ASD x CU traits | -0.1 | 0.25 | -0.6 | 0.4 | 1 | 1867 | 2075 |
| Interaction CD x CU traits | -0.23 | 0.23 | -0.68 | 0.22 | 1 | 1618 | 1997 |
| Affective Empathy | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% CI* | *u-95%* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | 0.05 | 0.27 | -0.5 | 0.58 | 1 | 2020 | 1996 |
| CD | -0.12 | 0.23 | -0.6 | 0.32 | 1 | 1849 | 2051 |
| CU traits | -0.12 | 0.18 | -0.47 | 0.22 | 1 | 1249 | 1668 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Interaction ASD x CU traits | -0.2 | 0.24 | -0.67 | 0.27 | 1 | 1607 | 1858 |
| Interaction CD x CU traits | -0.01 | 0.22 | -0.46 | 0.44 | 1 | 1445 | 1800 |
| **Parent-report** | | | | | | | |
| Cognitive Empathy | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% CI* | *u-95%* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | -0.75 | 0.26 | -1.27 | -0.22 | 1 | 2005 | 1678 |
| CD | -0.37 | 0.23 | -0.85 | 0.1 | 1 | 1846 | 1923 |
| CU traits | -0.21 | 0.18 | -0.55 | 0.14 | 1 | 1439 | 1722 |
| Interaction ASD x CU traits | -0.39 | 0.25 | -0.89 | 0.08 | 1 | 1789 | 1701 |
| Interaction CD x CU traits | 0.03 | 0.22 | -0.41 | 0.46 | 1 | 1829 | 1815 |
| Affective Empathy | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% CI* | *u-95%* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | -0.13 | 0.3 | -0.72 | 0.46 | 1 | 2078 | 2267 |
| CD | 0.23 | 0.26 | -0.28 | 0.73 | 1 | 1643 | 2199 |
| CU traits | -0.24 | 0.2 | -0.63 | 0.16 | 1 | 1175 | 1548 |
| Interaction ASD x CU traits | -0.21 | 0.27 | -0.75 | 0.32 | 1 | 1473 | 1966 |
| Interaction CD x CU traits | 0.16 | 0.24 | -0.31 | 0.65 | 1 | 1437 | 1670 |

This table shows results of the Bayesian regression analysis including the interaction between group and CU traits. All models included group as regressor of interest and age, IQ, sex and data collection wave as covariates. All variables were standardized before the analysis. *Est. Error = Estimate Error, l-95% CI = credible interval lower bound , u-95% CI = credible interval upper bound, Rhat = potential scale reduction factor, Bulk_ESS = bulk effective sample size estimate, Tail_ESS = tail effective sample size estimate, ASD = group with autism spectrum disorder, CD = group with conduct disorder, CU traits = Callous-unemotional traits, sum score of the Inventory of Callous-Unemotional traits (Frick, 2017).*

*Supplementary Table 3.* Bayes regression models including the interaction of group and age on self- and parent-reported affective and cognitive empathy

| **Self-report** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Affective Empathy | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% CI* | *u-95% CI* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | 0.11 | 0.24 | -0.38 | 0.57 | 1 | 2060 | 1961 |
| CD | 0.03 | 0.2 | -0.36 | 0.44 | 1 | 2220 | 2032 |
| Age | -0.07 | 0.13 | -0.33 | 0.18 | 1 | 1949 | 1944 |
| CU traits | -0.22 | 0.09 | -0.39 | -0.05 | 1 | 3038 | 2050 |
| Interaction ASD x Age | 0.47 | 0.18 | 0.11 | 0.82 | 1 | 2123 | 2127 |
| Interaction CD x Age | -0.18 | 0.18 | -0.53 | 0.17 | 1 | 2128 | 2191 |
| Cognitive Empathy | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% CI* | *u-95% CI* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | -0.75 | 0.26 | -1.27 | -0.24 | 1 | 2307 | 2074 |
| CD | 0.12 | 0.22 | -0.33 | 0.56 | 1 | 2446 | 1875 |
| Age | 0.01 | 0.14 | -0.26 | 0.28 | 1 | 1977 | 2070 |
| CU traits | -0.17 | 0.09 | -0.35 | 0.01 | 1 | 2713 | 1909 |
| Interaction ASD x Age | -0.07 | 0.19 | -0.44 | 0.31 | 1 | 2118 | 2153 |
| Interaction CD x Age | -0.08 | 0.19 | -0.45 | 0.29 | 1 | 2199 | 2115 |
| **Parent-report** | | | | | | | |
| Affective Empathy | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% CI* | *u-95% CI* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | -0.18 | 0.28 | -0.73 | 0.37 | 1 | 2100 | 2067 |
| CD | 0.33 | 0.23 | -0.12 | 0.78 | 1 | 2388 | 2229 |
| Age | -0.09 | 0.14 | -0.37 | 0.19 | 1 | 1758 | 1782 |
| CU traits | -0.24 | 0.1 | -0.43 | -0.04 | 1 | 2612 | 2067 |
| Interaction ASD x Age | 0.26 | 0.21 | -0.14 | 0.67 | 1 | 1922 | 2211 |
| Interaction CD x Age | 0.03 | 0.2 | -0.37 | 0.42 | 1 | 2083 | 2070 |
| Cognitive Empathy | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% CI* | *u-95% CI* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | -0.78 | 0.26 | -1.29 | -0.27 | 1 | 2470 | 1765 |
| CD | -0.22 | 0.22 | -0.64 | 0.22 | 1 | 2697 | 2196 |
| Age | 0.13 | 0.13 | -0.13 | 0.38 | 1 | 2203 | 2222 |
| CU traits | -0.31 | 0.09 | -0.49 | -0.14 | 1 | 3281 | 2154 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Interaction ASD x Age | 0.04 | 0.19 | -0.33 | 0.41 | 1 | 2444 | 2469 |
| Interaction CD x Age | -0.07 | 0.19 | -0.44 | 0.29 | 1 | 2341 | 2280 |

This table shows the Bayes regression models of group, age, and group x age interaction on self-and parent- reported Empathy subscales affective and cognitive empathy. The control group was set as the reference group and all variables were standardized. *Est. Error = Estimate Error, l-95% Cl = credible interval lower bound , u-95% Cl = credible interval upper bound, Rhat = potential scale reduction factor, Bulk_ESS = bulk effective sample size estimate, Tail_ESS = tail effective sample size estimate, ASD = group with autism spectrum disorder, CD = group with conduct disorder, CU traits = Callous-unemotional traits, sum score of the Inventory of Callous-Unemotional traits (Frick, 2017), IQ = intelligence quotient.*

*Supplementary Table 4.* Bayes regression models including the interaction group and sex in self- and parent-reported cognitive and affective empathy

| Self-report | | | | | | | |
|---|---|---|---|---|---|---|---|
| Affective Empathy | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% CI* | *u-95% CI* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | -0.26 | 0.36 | -0.98 | 0.42 | 1 | 1943 | 2039 |
| CD | -0.1 | 0.31 | -0.7 | 0.51 | 1 | 1745 | 1605 |
| Sex (male) | -0.96 | 0.27 | -1.49 | -0.43 | 1 | 1773 | 2249 |
| CU traits | -0.19 | 0.09 | -0.37 | -0.01 | 1 | 3220 | 1966 |
| Interaction ASD x Sex | 0.53 | 0.42 | -0.3 | 1.38 | 1 | 1784 | 1986 |
| Interaction CD x Sex | 0.14 | 0.38 | -0.59 | 0.88 | 1 | 1591 | 1834 |
| Cognitive Empathy | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% CI* | *u-95% CI* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | -1.04 | 0.35 | -1.72 | -0.35 | 1 | 1872 | 2045 |
| CD | 0.03 | 0.31 | -0.54 | 0.63 | 1 | 1875 | 1935 |
| Sex (male) | -0.37 | 0.27 | -0.91 | 0.15 | 1 | 1561 | 1954 |
| CU traits | -0.17 | 0.09 | -0.35 | 0 | 1 | 2613 | 2097 |
| Interaction ASD x Sex | 0.53 | 0.43 | -0.34 | 1.34 | 1 | 1731 | 1951 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Interaction CD x Sex | 0.2 | 0.38 | -0.56 | 0.94 | 1 | 1664 | 2091 |
| Parent-report | | | | | | | |
| Affective Empathy | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% CI* | *u-95% CI* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | -0.24 | 0.39 | -0.97 | 0.53 | 1 | 1839 | 2056 |
| CD | 0.3 | 0.34 | -0.39 | 0.97 | 1 | 1906 | 2028 |
| Sex (male) | -0.16 | 0.29 | -0.75 | 0.42 | 1 | 1666 | 2050 |
| CU traits | -0.22 | 0.09 | -0.41 | -0.04 | 1 | 2798 | 2248 |
| Interaction ASD x Sex | 0.02 | 0.46 | -0.88 | 0.91 | 1 | 1765 | 1800 |
| Interaction CD x Sex | -0.02 | 0.41 | -0.81 | 0.81 | 1 | 1725 | 1953 |
| Cognitive Empathy | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% CI* | *u-95% CI* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | -0.86 | 0.35 | -1.56 | -0.19 | 1 | 1470 | 1584 |
| CD | -0.1 | 0.31 | -0.7 | 0.5 | 1 | 1438 | 1922 |
| Sex (male) | -0.15 | 0.27 | -0.68 | 0.39 | 1 | 1410 | 2000 |
| CU traits | -0.31 | 0.09 | -0.48 | -0.14 | 1 | 2721 | 2004 |
| Interaction ASD x Sex | 0.11 | 0.42 | -0.71 | 0.92 | 1 | 1382 | 2025 |
| Interaction CD x Sex | -0.18 | 0.38 | -0.96 | 0.58 | 1 | 1284 | 1840 |

This table shows results of the Bayesian regression analysis including the interaction between group and sex. All models included group as regressor of interest and age, IQ, sex and data collection wave as covariates. All variables were standardized before the analysis. *Est. Error = Estimate Error, l-95% Cl = credible interval lower bound , u-95% Cl = credible interval upper bound, Rhat = potential scale reduction factor, Bulk_ESS = bulk effective sample size estimate, Tail_ESS = tail effective sample size estimate, ASD = group with autism spectrum disorder, CD = group with conduct disorder, CU traits = Callous-unemotional traits, sum score of the Inventory of Callous-Unemotional traits (Frick, 2017).*

*Supplementary Table 5.* Bayes regression models using discrepancy measures between self- and parent- reported affective and cognitive empathy

| **Affective Empathy** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Basic model | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% CI* | *u-95% CI* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | 0.31 | 0.32 | -0.32 | 0.95 | 1 | 2173 | 2348 |
| CD | -0.29 | 0.25 | -0.79 | 0.19 | 1 | 2245 | 2353 |
| Age | 0.02 | 0.1 | -0.17 | 0.21 | 1 | 3108 | 2088 |
| IQ | -0.03 | 0.11 | -0.24 | 0.18 | 1 | 2779 | 1972 |
| Sex (male) | -0.61 | 0.21 | -1.04 | -0.19 | 1 | 2762 | 2363 |
| Data collection wave | -0.25 | 0.24 | -0.72 | 0.22 | 1 | 2340 | 2083 |
| Including CU traits as covariate | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% CI* | *u-95% CI* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | 0.25 | 0.34 | -0.41 | 0.93 | 1 | 1936 | 1901 |
| CD | -0.35 | 0.28 | -0.91 | 0.2 | 1 | 1981 | 1873 |
| CU traits | 0.05 | 0.12 | -0.18 | 0.27 | 1 | 2504 | 2072 |
| Age | 0.01 | 0.1 | -0.2 | 0.2 | 1 | 3183 | 2538 |
| IQ | -0.03 | 0.11 | -0.25 | 0.18 | 1 | 2963 | 2213 |
| Sex (male) | -0.62 | 0.22 | -1.04 | -0.21 | 1 | 2714 | 2068 |
| Data collection wave | -0.25 | 0.24 | -0.7 | 0.22 | 1 | 2413 | 2387 |
| Interaction Group x CU traits | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% CI* | *u-95% CI* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | 0.2 | 0.36 | -0.51 | 0.89 | 1 | 2163 | 1995 |
| CD | -0.33 | 0.32 | -0.96 | 0.29 | 1 | 1977 | 2249 |
| CU traits | 0.1 | 0.25 | -0.37 | 0.58 | 1 | 1090 | 1851 |
| Age | 0 | 0.1 | -0.19 | 0.2 | 1 | 4280 | 2503 |
| IQ | -0.02 | 0.11 | -0.24 | 0.2 | 1 | 3398 | 2082 |
| Sex (male) | -0.63 | 0.22 | -1.06 | -0.2 | 1 | 3402 | 2084 |
| Data collection wave | -0.27 | 0.24 | -0.76 | 0.17 | 1 | 3008 | 2203 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Interaction ASD x CU traits | 0.03 | 0.33 | -0.64 | 0.65 | 1 | 1434 | 2087 |
| Interaction CD x CU traits | -0.15 | 0.3 | -0.75 | 0.44 | 1 | 1386 | 2122 |
| **Cognitive Empathy** | | | | | | | |
| Basic model | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% Cl* | *u-95% Cl* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | 0.19 | 0.33 | -0.47 | 0.85 | 1 | 2053 | 1981 |
| CD | 0.5 | 0.26 | -0.01 | 1.01 | 1 | 2246 | 1909 |
| Age | -0.15 | 0.1 | -0.34 | 0.06 | 1 | 2944 | 2179 |
| IQ | -0.17 | 0.11 | -0.38 | 0.05 | 1 | 2928 | 2203 |
| Sex (male) | 0.04 | 0.22 | -0.39 | 0.48 | 1 | 2783 | 2202 |
| Data collection wave | -0.24 | 0.23 | -0.7 | 0.22 | 1 | 2387 | 2050 |
| Including CU traits as covariate | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% Cl* | *u-95% Cl* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | 0.06 | 0.37 | -0.63 | 0.79 | 1 | 2522 | 2189 |
| CD | 0.35 | 0.29 | -0.22 | 0.92 | 1 | 2255 | 2074 |
| CU traits | 0.14 | 0.13 | -0.1 | 0.39 | 1 | 2937 | 2387 |
| Age | -0.15 | 0.11 | -0.37 | 0.06 | 1 | 2789 | 2450 |
| IQ | -0.18 | 0.11 | -0.4 | 0.05 | 1 | 3097 | 1989 |
| Sex (male) | 0.03 | 0.23 | -0.42 | 0.47 | 1 | 3161 | 2450 |
| Data collection wave | -0.25 | 0.24 | -0.72 | 0.21 | 1 | 2809 | 2459 |
| Interaction Group x CU traits | | | | | | | |
| | *Estimate* | *Est.Error* | *l-95% Cl* | *u-95% Cl* | *Rhat* | *Bulk_ESS* | *Tail_ESS* |
| ASD | -0.09 | 0.38 | -0.82 | 0.66 | 1 | 2173 | 2327 |
| CD | 0.44 | 0.32 | -0.21 | 1.09 | 1 | 1877 | 2024 |
| CU traits | 0.19 | 0.25 | -0.29 | 0.71 | 1 | 1593 | 1958 |
| Age | -0.18 | 0.1 | -0.38 | 0.02 | 1 | 4029 | 2226 |
| IQ | -0.13 | 0.12 | -0.35 | 0.1 | 1 | 4037 | 1945 |
| Sex (male) | 0.01 | 0.22 | -0.42 | 0.45 | 1 | 4096 | 2268 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Data collection wave | -0.26 | 0.24 | -0.73 | 0.2 | 1 | 3111 | 2118 |
| Interaction ASD x CU traits | 0.29 | 0.35 | -0.41 | 0.99 | 1 | 1870 | 2085 |
| Interaction CD x CU traits | -0.27 | 0.31 | -0.88 | 0.35 | 1 | 1958 | 1895 |

This table shows the Bayes regression models of groups and CU traits on self- and parent-reported discrepancy measures of affective and cognitive empathy subscales. The control group was set as the reference group and all variables were standardized. *Est. Error = Estimate Error, l-95% CI = credible interval lower bound , u-95% CI = credible interval upper bound, Rhat = potential scale reduction factor, Bulk_ESS = bulk effective sample size estimate, Tail_ESS = tail effective sample size estimate, ASD = group with autism spectrum disorder, CD = group with conduct disorder, CU traits = Callous-unemotional traits, sum score of the Inventory of Callous-Unemotional traits (Frick, 2017), IQ = intelligence quotient.*

*Supplementary Table 6.* Region of Interest Analysis Depicting Peak Clusters Negatively Associated with Callous-Unemotional Traits, Separated for Both Models

| Structures | Volume | Peak MNI Coordinates | | | t | log p value |
|---|---|---|---|---|---|---|
| | | X | Y | Z | | |
| *BES* | | | | | | |
| Anterior cingulate (L), Anterior cingulate (R), Medial orbitofrontal cortex (R) | 1323 | -1 | 44 | 3 | 3.81 | 1.96 |
| Mid-cingulate (L), Anterior cingulate (L), Mid-cingulate (R), Anterior cingulate (R) | 828 | -6 | 10 | 40 | 3.69 | 1.62 |
| Mid cingulate (L) | 448 | -10 | -20 | 39 | 3.45 | 1.5 |
| Anterior cingulate (L), Anterior cingulate (R) | 184 | -2 | 35 | 23 | 3.53 | 1.43 |
| Precuneus (R), Mid-cingulate (R) | 112 | 11 | -44 | 48 | 3.47 | 1.37 |
| *GEM* | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Anterior cingulate (L/R), Mid-cingulate (L/R), Medial orbitofrontal cortex (R) | 5196 | -1 | 43 | -3 | 4.81 | 2.6 |
| Precuneus (R), Mid-cingulate (L), Precuneus (R), Mid-cingulate (R) | 2360 | 11 | -42 | 48 | 3.61 | 1.73 |
| Calcarine (R), Precuneus (R), Cuneus (R) | 340 | 13 | -57 | 17 | 3.34 | 1.37 |

This table depicts detailed results of the main analysis investigating associations between GMV and CU traits across all participants. The presented clusters are significantly negatively associated with CU traits within the specified regions of interest and separated for both models including empathy scores from either the self-reported BES or the other-reported GEM. Regressions included group as factor, AE and CE of either the BES or the GEM, and total CU scores as regressors, as well as IQ, age, sex, data collection wave, and TIV as covariates. All included variables were z-scored. Results were estimated using TFCE, FWE-corrected, and thresholded at $p < 0.05$. As part of the TFCE-correction procedure, p-values were log-transformed, with 1.3 representing a p-value < 0.05, and 2 representing a p-value <0.01 (see CAT12 manual or https://neuro-jena.github.io/cat12-help/). Both models show an overlap in the main negative associations between CU traits and GMV in the ACC, extending into the vmPFC and the MCC, as well as the PCU. CU = Callous-Unemotional traits, BES = Basic Empathy Scale, GEM = Griffith Empathy Measure, GMV = Gray Matter Volume, FWE = Family-wise error correction for multiple comparisons, TFCE = Threshold Free Cluster Enhancement, ACC = Anterior Cingulate Cortex, vmPFC = ventromedial Prefrontal Cortex, MCC = Mid Cingulate Cortex, PCu = Precuneus, MNI =Montreal Neurological Institute, R = Right, L = Left.

*Supplementary Table 7*. Peak Clusters Significantly Negatively Associated with Callous-Unemotional Traits Across All Participants in a Whole-Brain Analysis

| Structures | Volume | Peak MNI Coordinates | | | t | log p value |
|---|---|---|---|---|---|---|
| | | X | Y | Z | | |
| BES | | | | | | |
| Anterior cingulate (L), Medial orbitofrontal cortex (R), Anterior cingulate (R), Medial frontal cortex (L), Medial superior frontal cortex (R), Rectus (L), Superior orbitofrontal cortex (R), Inferior orbitofrontal cortex (R) | 5106 | -1 | 45 | -2 | 5.08 | 2.17 |
| Mid-orbitofrontal cortex (L), Superior orbitofrontal Cortex (L), Rectus (L), Superior orbitofrontal cortex (R), Inferior orbitofrontal cortex (L), Medial orbitofrontal cortex (L) | 3924 | -28 | 58 | -17 | 3.66 | 1.5 |
| Mid cingulate (L), Supplementary motor area (L), Paracentral Lobule (L) | 1279 | -10 | -19 | 48 | 4.02 | 1.5 |
| Mid cingulate (L), Anterior cingulate (L), Mid cingulate (R) | 696 | -6 | 11 | 39 | 3.68 | 1.39 |
| Precuneus (R), Superior parietal lobule (R), Postcentral (R), Paracentral lobule (R) | 258 | 11 | -46 | 67 | 3.52 | 1.34 |
| Rectus (L), Inferior orbitofrontal (L), Mid orbitofrontal (L), Superior orbitofrontal (L), Rectus (L) | 476 | -15 | 33 | -14 | 3.35 | 1.33 |
| Precuneus (R), Mid cingulate (R) | 123 | 11 | -44 | 48 | 3.47 | 1.32 |
| GEM | | | | | | |
| Anterior and mid- (L) cortex, cingulate Anterior cingulate (R), Mid-orbitofrontal cortex (R), Precuneus (R), Superior orbitofrontal cortex (L), Rectus (L, R), Mid-cingulate (R), Medial orbitofrontal cortex (L), Superior orbitofrontal cortex (R) | 28540 | 0 | 45 | -2 | 4.06 | 2.42 |

This table depicts the clusters significantly negatively associated with CU traits as result of a whole-brain analysis, separated for both models including empathy scores from either the self-

reported BES or the other-reported GEM. Regressions included group as factor, AE and CE of either the BES or the GEM, and total CU trait scores as regressors, as well as IQ, age, sex data collection wave, and TIV as covariates. All included variables were z-scored. Results were estimated using TFCE, FWE-corrected, and thresholded at $p < 0.05$. Due to the TFCE-correction, p-values were log-transformed, with 1.3 representing a p-value < .05, and 2 representing a p-value <.01 (see CAT12 manual or https://neuro-jena.github.io/cat12-help/). Across all participants and in both models, significant negative associations were observed between GMV and CU traits in the ACC extending into the MCC and the vmPFC. Additionally, for the BES, the orbitofrontal pole was negatively associated with CU traits. *CU = Callous-Unemotional traits, BES = Basic Empathy Scale, GEM = Griffith Empathy Measure, GMV = Gray Matter Volume, FWE = Family-wise error correction for multiple comparisons, TFCE = Threshold Free Cluster Enhancement, MNI = Montreal Neurological Institute, R = Right, L = Left.*

*Supplementary Table 8*. Peak Clusters of the Region of Interest Analysis Investigating GMV Differences in Subgroups based on Callous-Unemotional Traits: Cutoff by Docherty et al. (2017)

| Contrast | Structures | Volume | Peak MNI Coordinates | | | *t* | log *p* value |
|---|---|---|---|---|---|---|---|
| | | | X | Y | Z | | |
| *BES* | | | | | | | |
| TD > low CU subgroup | Anterior cingulate (L) | 261 | -6 | 25 | 22 | 2.84 | 1.39 |
| TD > high CU subgroup | Anterior cingulate (L,R), Mid-cingulate (L,R), | 1849 | -6 | 12 | 32 | 3.34 | 1.74 |
| | Insula (R), Putamen (R) | 1837 | 38 | 0 | -15 | 3.21 | 1.68 |
| | Amygdala (R), Hippocampus (R), Parahippocampus (R) | 893 | 32 | 0 | -17 | 3.37 | 1.62 |
| | Mid-cingulate (L) | 383 | -7 | -31 | 40 | 3.74 | 1.62 |
| | Insula (L) | 258 | -32 | 3 | 12 | 2.56 | 1.36 |
| Low CU subgroup > high CU subgroup | Precuneus (R,L), Posterior cingulate (L) | 4599 | 5 | -64 | 51 | 3.26 | 1.52 |
| | Mid-cingulate (L) | 2570 | -1 | -17 | 37 | 2.88 | 1.47 |
| *GEM* | | | | | | | |
| TD > low CU subgroup | Anterior cingulate (L), Mid -ingulate (L) | 1271 | -6 | 22 | 26 | 3.07 | 1.71 |
| | Inferior parietal cortex (L) | 69 | -49 | -36 | 44 | 3.27 | 1.44 |
| TD > high CU subgroup | Insula (R), Putamen (R) | 1382 | 36 | 2 | -12 | 3.46 | 1.58 |
| | Anterior cingulate (L), Mid-cingulate (L) | 585 | -6 | 13 | 32 | 3.31 | 1.38 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Amygdala (R), Hippocampus (R) | 419 | 32 | 0 | -19 | 3.42 | 1.47 |
| | Mid-cingulate (L) | 277 | -7 | -30 | 40 | 3.68 | 1.47 |
| | Insula (L) | 63 | -38 | -1 | 0 | 2.66 | 1.33 |
| | Insula (L) | 66 | -40 | 11 | -12 | 2.82 | 1.32 |
| Low CU subgroup > high CU subgroup | Precuneus (R,L), Posterior cingulate (L), Calcarine (L), Mid cingulate (R) | 9620 | 5 | -64 | 52 | 3.49 | 1.84 |
| | Mid-cingulate (L,R), Anterior cingulate (L) | 4225 | -4 | -22 | 37 | 3.73 | 1.85 |
| | Precuneus (R,L), Posterior cingulate (L), Calcarine (L), Mid-cingulate (R) | 80 | 35 | 4 | 12 | 3.16 | 1.32 |

This table depicts peak MNI coordinates of GMV structures significantly differing between CU trait subgroups, separated for models including empathy scores of either the self-reported BES or the other-reported GEM. To form subgroups of patients with low and high CU traits, we used the clinical cutoff score of 30 as recommended by Docherty et al. (2017) for the parent-rated ICU. Therefore, the patient population was divided into a high (N =36) and a low (N = 49) CU trait subgroup, while the TD group (N = 45) remained the same (Ibrahim et al., 2021). The models were again separated for empathy scores obtained from either the self-reported BES or the other-reported GEM and contained CU subgroups as factor, AE and CE from either the BES or the GEM as regressor, as well as IQ, age, sex, data collection wave, and TIV as covariates. All included variables were z-transformed. Results were estimated using TFCE, FWE-corrected, and thresholded at $p < 0.05$. As part of the TFCE procedure, *p*-values were log-transformed, with 1.3 representing a *p*-value < 0.05, and 2 representing a *p*-value <0.01 (see CAT12 manual or https://neuro-jena.github.io/cat12-help/). To investigate potential group differences, contrasts between the three groups TD, high CU patient subgroup, and low CU patient subgroup were analyzed. Results show significant differences in all three contrasts for both models, in part overlapping with the main results in the association between CU traits and GMV across all participants. In addition, the high CU patient subgroup shows significantly lower GMV in the amygdala, the insula, and the hippocampus, relative to the TD group. *MNI = Montreal Neurological Institute, GMV = Gray Matter Volume, CU = Callous-Unemotional*

*traits, BES = Basic Empathy Scale, GEM = Griffith Empathy Measure, ICU = Inventory of Callous-Unemotional Traits, TD = Typically Developing youth, AE = Affective Empathy, CE = Cognitive Empathy, TIV = Total Intracranial Volume, TFCE = Threshold Free Cluster Enhancement, FWE = Family-wise error correction for multiple comparison within region of interest, R = Right, L = Left.*

*Supplementary Table 9.* Comparison of Subscale Reliabilities for self- and parent reported questionnaires using Cronbach's alpha

| | Self-report | | | | Parent report | | | |
|---|---|---|---|---|---|---|---|---|
| *Subscale* | *Cronbach's alpha* | *No. Items* | *M* | *SD* | *Cronbach's alpha* | *No. Items* | *M* | *SD* |
| Affective Empathy | 0.74 | 11 | 2.9 | 0.65 | 0.96 | 9 | 2.3 | 3.1 |
| Cognitive Empathy | 0.76 | 9 | 3.5 | 0.65 | 0.86 | 6 | 2.2 | 2.2 |

This table shows the results of the internal consistency analysis using Cronbach's alpha on AE and CE subscales for the self-and parent reported questionnaires Basic Empathy Scale (BES) and Griffith Empathy Measure (GEM). AE and CE subscales for both questionnaires revealed good internal consistencies with self-reports showing over 0.7 and parent reports showing over 0.8 for CE and over 0.9 for AE. *Cronbach's Alpha = scale reliability measure, No. Items = number of items within a subscale, M = mean, SD = stan*

## Appendix C: Supplementary Material Study 3

Supplementary Table S1. Results of multi-level regression analyses on RSA

| | *Estimate* | *Std. Error* | *df* | *t-value* | *p-value* |
|---|---|---|---|---|---|
| Age | -0.132 | 0.029 | 1429.000 | -4.516 | < 0.001 |
| Sex | 0.005 | 0.028 | 1429.000 | 0.171 | 0.864 |
| BMI | 0.023 | 0.028 | 1429.000 | 0.830 | 0.407 |
| SES | -0.029 | 0.027 | 1429.000 | -1.073 | 0.284 |
| Cigarettes/day | -0.056 | 0.028 | 1429.000 | -2.006 | 0.045 |
| Sports (h)/week | 0.034 | 0.027 | 1429.000 | 1.267 | 0.206 |
| PNS Medication intake | -0.081 | 0.027 | 1429.000 | -3.022 | 0.003 |

This table shows the results of the multilevel regression analysis including variables possibly influencing RSA based on previous findings in the literature (e.g. Prätzlich et al., 2019; Oldenhof et al., 2019). The following independent variables were included in the model as fixed effects: Age, sex, BMI (Body-Mass-Index), SES = Socio economic status based on parental income, education and occupation, cigarettes smoked per day, sports hours per week, medication intake and as random effect: site. Std. Error = Standard Error, df = degrees of freedom. Significance level = $p < 0.05$. Results showed significant negative effects of age, cigarettes and medication intake on RSA.

Supplementary Table S2. Group differences in Correct Responses and Reaction Time

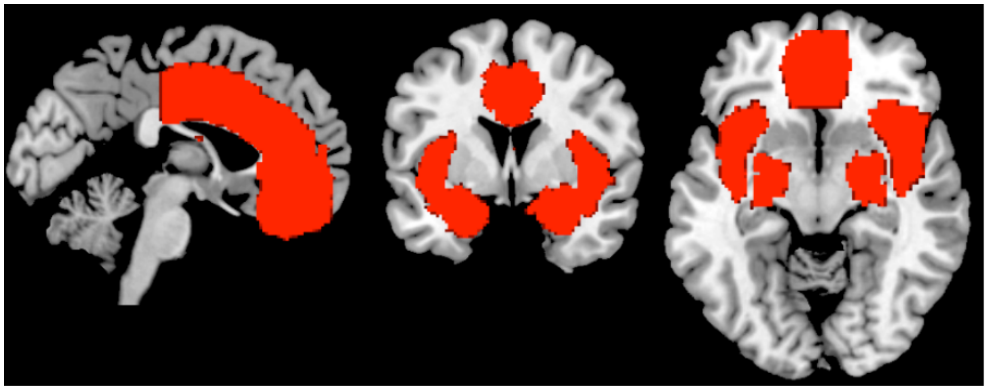
| | **TD (N=753)** | **CD (N=693)** | *t-value* | *p-value* |
|---|---|---|---|---|
| | *Mean (SD)* | *Mean (SD)* | | |
| Correct response rate Cognitive Regulation | 68.746 (1.946) | 64.463 (2.066) | -13.245 | < 0.001 |
| Reaction time Cognitive Regulation | 422.499 (62.283) | 423.134 (71.282) | -240.68 | < 0.001 |
| Correct response rate Emotion Regulation | 66.585 (1.844) | 60.256 (2.048) | -11.063 | < 0.001 |
| Reaction time Emotion Regulation | 428.626 (72.073) | 424.774 (67.89) | -231.24 | < 0.001 |

This table shows group differences between adolescents with CD diagnosis compared to TDs in RSA and performance measures in the Go/NoGo task which are reaction times to Go trials and proportion of correct response rates to NoGo trials (1- incorrect response rate to NoGo trials) during the emotion regulation and cognitive regulation condition of the Emotional Go/NoGo task. Correct response rate to NoGo trials (%), Reaction time (ms). Significance level = $p < 0.05$. The TD group shows both higher correct response rates and shorter reaction times than the CD group during cognitive regulation trials. During emotion regulation trials the TD group shows higher correct response rates and longer reaction times than the CD group.

Supplementary Table S3: Results of multi-level regression analyses on task performance measures in the subsample with T1 imaging data (N=577)

| IES Cognitive Control | | | | | |
|---|---|---|---|---|---|
| | *Value* | *Std.Error* | *DF* | *t-value* | *p-value* |
| RSA | -0.101 | 0.160 | 563.000 | -0.628 | 0.530 |
| Group | -0.391 | 0.209 | 563.000 | -1.866 | 0.063 |
| Age | -0.011 | 0.170 | 563.000 | -0.065 | 0.948 |
| Interaction RSAxGroup | -0.112 | 0.160 | 563.000 | -0.700 | 0.484 |
| IES Emotion Control | | | | | |
| | *Value* | *Std.Error* | *DF* | *t-value* | *p-value* |
| RSA | -9.217 | 17.409 | 562.000 | -0.529 | 0.597 |
| Group | -24.600 | 22.622 | 562.000 | -1.087 | 0.277 |
| Age | -139.454 | 18.479 | 562.000 | -7.546 | 0.000 |
| Interaction RSAxGroup | -14.579 | 17.424 | 562.000 | -0.837 | 0.403 |

This table shows the relationship between RSA and the different dependent variables in the study in the subsample of participants included in the imaging analysis. Key task performance measures were Inverse Efficiency Scores (IES) as speed-accuracy trade off scores of z-transformed mean reaction time (Go trials) and z-transformed correct response rate to NoGo trials (1-incorrect response rate to NoGo trials) in the emotion regulation and cognitive regulation conditions of the task. Models included additional fixed effects to control covariates for ADHD diagnosis, age, IQ, SES, sex, number of cigarettes smoked per day and as random effect site. All questionnaire scores were t-scored and centered, and all variables included in the model were z-transformed. RSA = Respiratory Sinus Arrhythmia measure at baseline, Group = difference between patient group CD and control group TD (reference group = TD), Std. Error = Standard Error, df = degrees of freedom. Significance level = $p < 0.05$. No significant associations were found between RSA or RSA x Group interactions on task performance measures.



Supplementary Figure S1. Masked regions of the CAN (Central Autonomic Network)

For a Region Of Interest (ROI) analysis we created a mask consisting of regions of the CAN which regulate ANS activity but are also involved in emotional and cognitive self-regulation processes (i.e., amygdala, insular cortex, anterior cingulate cortex & ventromedial prefrontal cortex).