EMOTION PROCESSING, PSYCHOPHYSIOLOGY AND BRAIN VOLUME IN MALTREATED YOUTH. MARKERS OF LATENT VULNERABILITY AND RESILIENCE

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ABSTRACT

The aim of this thesis was to explore differences in emotion processing, psychophysiology, and brain structure, in children and adolescents with experiences of childhood maltreatment with versus without psychopathology. Chapter 3 investigated emotion recognition and learning, indicating that maltreated youth without psychopathology were less accurate than non-maltreated youth when recognizing happiness, fear, and disgust. Similarities and differences were also observed between sexes, whereby males and females exhibited reduced recognition for fear, but females showed an impairment for happy faces, and males for disgust. For emotion learning, maltreated girls were worse at learning from punishment compared to non-maltreated girls, and maltreated boys were better than non-maltreated boys. Chapter 4 focused on parasympathetic and sympathetic nervous system functioning, showing that in the absence of psychopathology, maltreated youth exhibited increased heart rate variability (HRV) than non-maltreated youth, and increased electrodermal activity (EDA) irrespective of psychopathology levels. Chapter 5 explored brain structure, showing that when psychopathology was present, maltreated males had increased volume in the caudate compared to non-maltreated males, whereas maltreated females exhibited reduced volume in this region compared to non-maltreated females. Taken together, these findings highlight the importance of accounting for co-morbid psychopathology and exploring sex differences in studies of childhood maltreatment, while extending our understanding of latent vulnerability and resilience.

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KEY ABBREVIATIONS

ACE	Adverse Childhood Experience
ANS	Autonomic Nervous System
CM	Childhood Maltreatment
ASPD	Antisocial Personality Disorder
BPD	Borderline Personality Disorder
CBCL	Child Behaviour Checklist
CBE	Children's Bad Experiences Questionnaire
CD	Conduct Disorder
CD-RISC	Connor Davidson Resilience Scale
CNS	Central Nervous System
CRPBI	Child Report of Parent Behaviour Inventory
EDA	Electrodermal Activity
ELS	Early Life Stress
GMV	Grey Matter Volume
K-SADS-PL	Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime
OFC	Orbitofrontal Cortex
PDS	Pubertal Development Scale
PFC	Prefrontal Cortex
PMQ	Parental Monitoring Questionnaire
ROI	Region of Interest
SES	Socioeconomic Status
SMA	Somatosensory Area

Chapter 1

CHAPTER 1: INTRODUCTION TO CHILDHOOD MALTREATMENT

1.1 Thesis overview

"Most of my memories were of a loud angry household. My most vivid childhood memories were of my mother screaming at me, calling me names, and putting me down. Occasionally, she would hit us. When she did, she would be so angry that she would lose control. When she would get angry with me, she would yell and call me names, purposely being hurtful.

My first such memory was when I was 5 years old. We were getting ready for church, and I was unable to find one of my shoes. When I told my mother, she yelled and screamed that I had misplaced the shoe on purpose so that I wouldn't have to go to church. On the way to church, she continued by telling me that I was the devil and I had nothing but evil in me. In the fourth grade, I went to a new school. For the first four or five months, I was picked on and bullied. When I told my mother, her first response was to ask me what I had done to make them pick on me. It was about this time that I began to believe that I was less than, not as good as, other kids.

I carried that feeling into adulthood, and still fight with it today." (Goodwin-Slater, 2019)

Experiences of childhood maltreatment such as the one described above have an alarming global prevalence of up to 36%, depending on whether they are self- or child protection services (CPS)- reported (Stoltenborgh et al., 2015). Moreover, the conditions caused by the Coronavirus pandemic, such as isolation, financial insecurity, increased stressors for the caregivers, and reduced interactions with safeguarding services, have heightened the vulnerability of children and young people to maltreatment (Roumanou & Belton, 2020). The economic costs are immense. In the UK, the average lifetime cost of non-fatal childhood maltreatment is estimated between £89,390 to £145,508, and £940,758 for fatal maltreatment (Conti et al., 2021). Globally, child maltreatment associated costs are estimated at $3.7 trillion or 4.3% of global GDP (World Health Organization, 2019).

More importantly, exposure to abuse and neglect during childhood and adolescence can carry long-term developmental consequences (Herrenkohl et al., 2013). Prospective longitudinal studies show that childhood maltreatment is linked to various problems in adolescence and adulthood. These include the emergence of diagnoses and symptoms of mental health disorders, substance misuse and addiction, and compromised physical health (Bonomi et al., 2008; P. Cohen et al., 2001; Shonkoff et al., 2009; Widom et al., 1995). Indeed, it has been shown that maltreatment and psychopathology are so often co-occurring, that only 1.5% of maltreated individuals function well despite this adversity (Cicchetti & Rogosch, 1997a). Notwithstanding this high co-morbidity, few studies account for the presence of psychopathology when investigating childhood maltreatment (Dennison et al., 2019a; Kasparek et al., 2020; Saarinen et al., 2021; Sigrist et al., 2021; W. Yang et al., 2023). Given that both internalizing and externalizing psychopathologies are associated with neurocognitive functioning (Beauchaine, 2015; de Looff et al., 2022; Goodkind et al., 2015; Porter et al., 2020), these investigations create a challenge in separating the origin of these alterations. Moreover, sex differences are often understudied in childhood maltreatment, despite evidence that males and females respond differently to stress (Bangasser & Wiersielis, 2018; Kudielka & Kirschbaum, 2005). Thus, disentangling the source of alterations following childhood maltreatment, and accounting for sex effects, is of paramount importance not only for advancing research in this field, but also for prevention and intervention strategies.

In this thesis, I explored distinct associations of maltreatment and psychopathology, and interactive effects on three domains (i.e., emotion processing – facial emotion recognition and learning, autonomic nervous system functioning (ANS), and brain structure) by separating youth with and without maltreatment into groups with versus without psychopathology. As a result, the objective is to empirically investigate whether youth who experienced childhood maltreatment carry markers of latent vulnerability in emotion recognition, emotion learning, ANS functioning, and cortical and subcortical volume, even before psychopathological symptoms become apparent. Importantly, by studying maltreated youth without psychopathology, I also aimed to identify potential markers of resilience, which may indicate adaptive functioning despite experiences of abuse and/or neglect. Finally, I also explored moderating effects of sex on the associations between maltreatment and psychopathology with the three domains.

Chapter 1 will introduce childhood maltreatment, including definitions, prevalence, risk and protective factors, and main theoretical frameworks of neurodevelopment following maltreatment. Then, I will introduce the two key concepts that motivated this thesis : latent vulnerability and resilience following maltreatment. Finally, I will give an overview of the three domains explored in this thesis – emotion processing, ANS functioning, and brain volume, highlighting gaps in the literature which I suggest are partly due to co-morbid psychopathology and unexplored sex differences.

1.2 Definition and subtypes

Childhood maltreatment (CM) is described as exposure to abuse and/or neglect under the age of 18. CM comprises three subtypes of abuse - physical, sexual and emotional, and two subtypes of neglect - emotional and physical. According to the World Health Organisation, physical abuse refers to harm resulting in non-accidental physical injury, typically by a caregiver or someone responsible for the child (World Health Organization, 1999). Sexual abuse refers to involvement of children in any sexual activity, that they are not developmentally prepared for, able to consent to or fully understand. Emotional abuse involves failure to provide an emotionally supportive environment, necessary for the child's development of emotional and social competencies. This can include humiliation, criticism, threatening, blaming or manipulation. Finally, physical and emotional neglect refer to failure of the caregiver to provide for the development of the child's physical health (e.g., nutrition, shelter, safe living conditions) and their emotional development (e.g., warmth, acceptance, positive reinforcement) (World Health Organization, 1999).

1.3 Prevalence

It is challenging to estimate how many children are exposed to CM worldwide. This is due to the absence of a clear "gold standard" for what constitutes maltreatment and how it can be measured (Moody et al., 2018). Despite these difficulties, one study provided an estimate of the global prevalence of CM by comparing a series of meta-analyses (N=244 publications) on the prevalence of various subtypes of maltreatment (Stoltenborgh et al., 2015). First, they found that prevalence rates from self-reported CM were strikingly higher than those from informant studies. Specifically, sexual abuse had a self-report prevalence rate of 18% in girls and 7.6% in boys, 22.6% for physical abuse, 36.3% for emotional abuse, 16.3% for physical neglect and 18.4% for emotional neglect (Stoltenborgh et al., 2015). However, when informant studies were used, the combined prevalence for sexual, physical and emotional abuse was as little as 0.4%, and rates for neglect could not be calculated due to a lack of sufficient studies. This finding is consistent with longitudinal studies linking self-report to official records, which show that only a small proportion of self-reported CM if officially recorded by Child Protection Services (Gilbert et al., 2009). This considerable discrepancy between self- and informant-based reports is due to the latter's failure to capture instances of abuse and/or neglect where no one has yet considered that action should be taken (Creighton, 1995). In other words, informant-based prevalence rates are a drastic underrepresentation of CM, including only the most severe cases, where chronicity and need for protection were officially recognised by professionals. Second, they highlight that CM research is predominantly focused on sexual abuse and that the least investigated subtypes of maltreatment are emotional abuse and neglect. This may be due to sexual abuse being considered more harmful for development (Hornor, 2010) and/or due to having clearer boundaries around what is considered right and wrong, as opposed to physical abuse, for instance, which is normalised in some cultures as parental disciplinarian behaviour (Durrant, 2008). Third, CM seems to be concentrated in Western cultures, with most studies being conducted in North America and Europe, yet conclusions are often generalised to the world population (Arnett, 2009). Taken together, these findings show that i) despite efforts on legislative, administrative, and educational fronts, CM is a global phenomenon more frequent than officially reported, ii) future research should make it a priority to combine informant- and self-report measures of maltreatment when possible, and iii) more work is needed to understand the incidence and consequences of emotional abuse and neglect in both Western and non-Western cultures.

1.4 Prospective and retrospective measures of maltreatment

Given the low between-method agreement of CM measurements (Baldwin et al., 2019), I will now turn to discuss the advantages and disadvantages of retrospective and prospective measures of maltreatment. Retrospective measures are the most commonly used as they provide a comprehensive overview of a person's experiences of abuse and/or neglect over their lifetime and are easier to obtain compared to official records. However, these heavily rely on memory and have been shown to be biased by current mental state (Colman et al., 2016), experiences in adulthood (Widom, 1999), and be subject to omission (Widom & Morris, 2007). For instance, one study found that when adults were asked by two separate interviewers about their (documented) experience of sexual abuse, 51% did not report their CM to either one or both interviewers (Spatz Widom et al., 2006). Moreover, due to the underdevelopment of the infant brain, which may lead to the so-called infantile amnesia, most individuals are not able to recollect episodic memories from the first two or three years of their life (Alberini & Travaglia, 2017). Indeed, a review by Hardt & Rutter, (2004) investigating the validity of adult retrospective reports of adverse experiences, suggests that retrospective recall involves a substantial rate of false negatives and measurement errors, and that reports of details of early experiences (e.g., sequence, timing) should be interpreted with caution. Nevertheless, they conclude that this bias is not sufficiently great to invalidate retrospective case-control studies, which are very useful in CM research (Hardt & Rutter, 2004).

Prospective measures, on the other hand, provide real-time information about the occurrence and development of childhood maltreatment, may reduce recall bias by capturing events as they occur (Widom et al., 1999) and provide more detailed and accurate information about the nature and extent of abuse or neglect experiences (Newbury et al., 2018). However, one important limitation is that they are typically limited to specific time periods, as opposed to retrospective measures, which cover entire lifetimes. Thus, prospective measures may not capture events that occurred prior to the study. Last but not least, these measures are usually more resource-intensive and challenging to implement, and have lower sensitivity, capturing only the most severe cased of CM. To conclude, prospective and retrospective measures of maltreatment seem to identify different groups of individuals, who may have different risk pathways to psychopathology (Francis et al., 2023). Given this, researchers should aim to combine self-reports and prospective measures, as well as clearly operationalised criteria for measuring CM subtypes.

1.5 Risk factors of maltreatment

An essential requirement for developing effective prevention strategies is a comprehensive understanding of risk factors, which includes experiences, behaviours, characteristics, and contexts that increase the probability of CM. The socioecological model has been proposed as a framework to comprehend the intricate connections between various broad and immediate factors that impact health and development (Bronfenbrenner, 1977). These nested environments consist of individual, interpersonal, community, and societal levels. At an individual level, child-like characteristics, such as age and special healthcare needs or disabilities, can increase a child's vulnerability to maltreatment. For instance, the National Child Abuse and Neglect Data System (NCANDS) showed that children under 1 year have the highest rate of maltreatment, with about 25.3 confirmed cases per 1000 children in 2017 (Wildeman et al., 2014). Moreover, a higher number of confirmed maltreatment cases is shown among those with conditions like Down syndrome (Van Horne et al., 2015, 2018), attention deficit hyperactivity disorder (ADHD) (Jaudes & Mackey-Bilaver, 2008) and conduct disorder (CD) (Fairchild et al., 2019) compared to unaffected children.

At the interpersonal level, well-established family risk factors for CM include poverty, parental mental health, substance use disorders, or intimate partner violence (IPV) (Farrington & Ttofi, 2021; Kepple, 2017; H. Kim & Drake, 2018; M.-Y. Yang, 2015). For instance, one study showed that housing and food insecurity were linked to a rise in maternal self-reported maltreatment behaviours (Marcal, 2018). Similarly, (Chemtob et al., 2013) showed that maternal PTSD and depressive symptoms were associated with self-reported acts of childhood abuse and neglect perpetrated on their own children, whereas paternal depression was associated with more instances of childhood neglect (S. J. Lee et al., 2012). Finally, parents of young children who engage in heavy drinking and illicit substance use show increased maltreatment behaviours (Kepple, 2017), and mothers experiencing IPV by a current partner are more likely to endorse aggression, spanking, and neglect (Taylor et al., 2009). Other interpersonal risk factors important for our understanding of potential interactions between maltreatment and psychopathology are maternal stress (Sandman et al., 2018) and alcohol consumption (Murray et al., 2016) during pregnancy, which are also linked to childhood-onset CD.

At community level, two risk factors have been most consistently identified in the empirical literature – neighbourhood crime and concentrated disadvantage (e.g., area level poverty, unemployment, housing foreclosure, and vacancy) (Daley et al., 2016). Higher unemployment rates are positively associated with risk of child neglect, and crime rates are positively associated with risk of physical and sexual abuse (Morris et al., 2019). These risk factors are also positively associated with CD (Fairchild et al., 2019). Finally, societal-level elements such as policies, trends, and norms have gained increased attention as potential risk factors for child maltreatment. Indeed, economic policies that reduce household incomes or increase regressive taxes have been associated with higher reports of maltreatment (Béland et al., 2021). Gender inequality is another societal-level risk factor, potentially increasing child abuse through limited opportunities for women and challenges in protecting their children (Klevens & Ports, 2017; Negriff et al., 2017). Last but not least, it is important to note that it is the cumulation, rather than the presence of a single risk factor, that is predictive of child maltreatment (M.-Y. Yang & Maguire-Jack, 2018). Moreover, the risk of maltreatment is most likely to increase exponentially, where risk factors interact and strengthen each other (Lamela & Figueiredo, 2018; Vial et al., 2020).

1.6 Consequences of maltreatment

Having seen the complexity of the interplay between risk factors of childhood maltreatment, I will now focus on their respective contribution to child development over time. Over the past four decades, considerable efforts have been made to understand the series of consequences that may develop after childhood experiences of abuse and neglect (Krugman & Korbin, 2022). Like the risk factors, these consequences can manifest across multiple domains of functioning, being strongly interconnected, and highlighting that early patterns of adaptation/maladaptation have a nonlinear influence on later adaptation. These domains include cognitive, social, behavioural, and mental and physical health outcomes.

1.6.1. Cognitive outcomes of childhood maltreatment

Numerous studies consistently demonstrate that childhood maltreatment poverty has detrimental effects on cognitive functioning and academic performance, which can persist from early childhood through adulthood (Masson, East-Richard, & Cellard, 2015). In a systematic review (N studies =17), (Irigaray et al., 2013) found that individuals who experienced childhood abuse, showed lower performance on tasks measuring verbal episodic memory, working memory, attention, and executive functions compared to non-abused individuals.

Similarly, (Cowell et al., 2015) showed that maltreated children exhibited poorer performance on inhibitory control and working memory tasks when compared to children who had not experienced maltreatment. Finally, two population-representative birth cohort studies (Danese et al., 2017), found that individuals exposed to childhood maltreatment exhibited impairments in various cognitive domains such as general intelligence, executive function, processing speed, memory, perceptual reasoning and verbal comprehension compared to non-maltreated groups. However, it was also found that these associations were considerably reduced by pre-existing cognitive deficits and genetic and environmental factors, suggesting that further work is needed to explore potential confounding factors (Danese et al., 2017).

1.6.2. Social and behavioural outcomes of childhood maltreatment

Maltreated children are known to display behavioural and social problems, including early reports of physical assaults and aggression in school. They are also at risk of developing conduct disorder, experiencing school problems, engaging in delinquency, and being involved in crime and violence during adolescence and young adulthood (Rogosch & Cicchetti, 1994). (Dodge et al., 1995), for instance, showed that children who experienced physical abuse were at higher risk of exhibiting externalizing problems, as reported by their parents, as opposed to children who did not have a history of abuse. (Manly et al., 2001) found that the severity of physical neglect in the preschool period was associated with internalizing symptoms and withdrawn behaviour, whereas another study showed that multiple subtypes of maltreatment, and an early onset, were associated with emotion dysregulation (Kim & Cicchetti, 2009). Moreover, emotion dysregulation at time 1 was linked to externalizing symptoms at time 1, which, in turn, contributed to peer rejection at time 2 (Kim & Cicchetti, 2009). In addition, extensive literature shows that physically maltreated children are at a higher risk of becoming perpetrators of abuse themselves (Widom, 1989), being incarcerated as juveniles and adults (Lansford et al., 2007), and are at a higher risk for prostitution (especially for sexually abused females) (Widom & Kuhns, 1996), revictimization (Li et al., 2019), and teenage pregnancy (Negriff et al., 2015). Last but not least, child abuse and neglect have also been linked to poor economic outcomes in adulthood. Findings from (Currie & Spatz Widom, 2010) revealed that adults with experiences of abuse and/or neglect have lower education attainment, employment rates, and lower earnings compared to matched controls, and that this effect was stronger for maltreated females.

1.6.3. Mental health outcomes of childhood maltreatment

In addition to cognitive and behavioural outcomes, maltreatment is strongly associated with poor mental health. Unsurprisingly, one of the most consistent findings is an increased risk for developing post-traumatic stress disorder (PTSD) (Copeland et al., 2007; De Bellis et al., 2010). The prevalence of PTSD in adults with documented histories of child maltreatment ranges from 30% to 38%, significantly higher than the 7% estimate in the general adult population (Kessler et al., 2005; Widom, 1999). Similarly, maltreated individuals are three times more likely to develop depression in adolescence (Brown et al., 1999), and are at a higher risk for a lifetime time diagnosis of depression (Widom et al., 2007) and suicidal behaviour (Harford et al., 2014). Moreover, meta-analyses reported that childhood maltreatment affects the course of the illness, and the treatment outcomes (Infurna et al., 2016; Nanni et al., 2002). Relatedly, childhood abuse has also been linked to alcohol and substance abuse. One longitudinal study found that maltreated females were at a higher risk for a diagnosis of alcohol dependence compared to non-maltreated females, but no effect was found for males (Widom et al., 1995). Abused and neglected children are also more likely to use illicit drugs in middle adulthood compared to controls (Spatz Widom et al., 2006), and maltreated females are at a greater risk of drug use compared to maltreated males (Cicchetti & Handley, 2019; Halpern et al., 2018). Finally, other longitudinal studies showed that childhood maltreatment is linked to four times a higher risk of developing personality disorders in adulthood. For instance, using a large sample (N = 1196), Widom (1998) showed a notable rise in the risk of antisocial personality disorder (ASPD) for both abused and neglected males and females when compared to same-sex controls, and a systematic review by (Ibrahim et al., 2018) showed that maltreated children are also more likely to develop borderline personality disorder (BPD). These findings are in line with a recent meta-analysis of epidemiological and prospective cohort studies, where patients diagnosed with BPD had a higher likelihood of reporting childhood adversity compared to other clinical populations (Porter et al., 2020). Finally, the most recent meta-analysis by (Baldwin et al., 2023) (N studies = 34) including 54,646 participants showed a small, causal contribution of childhood maltreatment to poor mental health.

1.6.4. Physical health associations with childhood maltreatment

While outside the scope of this thesis, it is important to note that maltreatment is associated with various negative physical health outcomes (Carr et al., 2020; Petruccelli et al., 2019). These include neurological, musculoskeletal, respiratory, cardiovascular, gastrointestinal, gynaecological, metabolic, sleep, psychosomatic disorders as well as a variety of pain conditions (Carr et al., 2020; Ho et al., 2020). For example, prospective longitudinal evidence (Herrenkohl et al., 2013) shows that children with welfare involvement were more inclined to describe their physical health as poor/fair, experienced more somatic symptoms, and had higher symptom severity when compared to a non-welfare comparison group. Similarly, in a study by (Johnson et al., 2017), neglect was a significant predictor of cardio-metabolic risk, self-reported health quality, and the number of health problems in adulthood.

1.7 Theoretical frameworks of neurodevelopment following childhood maltreatment

A natural question arising from these associations between CM and adverse outcomes is the mechanism through which these consequences manifest. Substantial research suggests that maltreated individuals exhibit alterations in various systems, including the immune, endocrine, cardiovascular, behavioural, central nervous system (Grassi-Oliveira et al., 2015). Below I will provide a brief overview of the most established theoretical frameworks of neurodevelopment following childhood maltreatment – the ecological-transactional (Bronfenbrenner, 1977; (Cicchetti & Toth, 2005), and the allostasis model (Juster et al., 2010; McEwen & Seeman, 1999; McEwen & Wingfield, 2010), followed by a more detailed account of the theory of latent vulnerability (McCrory, 2018; McCrory et al., 2017), a more recent model, and one of the main foci of this thesis.

As mentioned in section 1.5, disruptions in neurobiological development can be understood within the socioecological/ecological-transactional model (Cicchetti & Toth, 2005). According to this model, maltreatment is considered a traumatic event that occurs outside the expected and regular environment. Any significant deviation from stable conditions raises the likelihood of the developing psychopathology's trajectory being changed. Throughout early brain development, environmental influences continually shape and adjust cellular processes like synaptic plasticity, connectivity, and apoptosis (i.e., the natural death of cells) (Hebb, 1949). These external factors have a significant impact on how the brain's structure and functions evolve during this sensitive period, leading to a considerable amount of neurobiological abnormalities following early child maltreatment (Dannlowski et al., 2012; Teicher et al., 2016a).

Relatedly, the allostasis model focuses on the adaptation required from the child following experiences of maltreatment. When faced with adverse physical and psychological situations, the child is required to "achieve stability through change" (i.e., allostasis) via various physiological parameters (McEwen & Wingfield, 2010). Factors contributing to allostasis include alterations in behaviour, the central nervous system (CNS), agents involved in immune function (like cytokines), the hypothalamic-pituitary-adrenal (HPA) axis, and cardiovascular function (Grassi-Oliveira et al., 2015). When these adaptive mechanisms are frequently triggered, the organism begins to operate in an allostatic condition. The prolonged effect of being in an allostatic state is known as allostatic load (McEwen & Seeman, 1999). That is, if the energy needed to sustain allostatic load surpasses the energy gained, it leads to allostatic overload, imposing a significant toll on the organism, increasing the risk of psychopathology.

1.7.1 The theory of latent vulnerability

The theory of latent vulnerability emerged as a reaction to the imprecise comprehension of the ways in which maltreatment influences neurocognitive systems, potentially heightening the likelihood of developing subsequent psychopathological conditions (McCrory & Viding, 2015). The authors argue that research in child mental health has overly embraced the medical model, dedicating too much attention to the investigation of psychiatric disorders, and too little to the mechanisms linked to their development. Drawing from literature showing that individuals meeting the criteria for a particular diagnosis do not consistently share similarities (Hovens et al., 2009), and recognizing the distinctions between those with a psychiatric disorder and a history of maltreatment compared to those without maltreatment (Agnew-Blais & Danese, 2016), it has been proposed that maltreatment induces *detectable* changes in neurobiological systems, indicative of alterations to neglectful and/or abusive environments. An important characteristic of these alterations is that they carry adaptive value in early maladaptive environments, but that long-term, and in adaptive situations, they can incur a cost. That is, the individual can lose the ability to optimally respond to demands in non-threatening environments, increasing vulnerability to future stressors (McCrory et al., 2017). These indicators of latent vulnerability are characterised by three key features. First, these are not thought of as symptoms, but refer to cognitive processes and connected patterns of neural activation involved in the development of a disorder (e.g., altered response to reward cues may increase vulnerability to depression, but is not a symptom of this condition) (Dennison et al., 2016). Second, these markers are best described at a systems level. This means that latent vulnerability is characterised by a multifaceted phenotype, a maladaptive adaptation within higher order systems involved in socioemotional and cognitive operations. Third, the theory suggests that these markers can be identified before the emergence of psychiatric conditions, serving as predictive factors for future risk levels. Currently, evidence of latent vulnerability in maltreated children and adolescents comes from studies using magnetic resonance imaging to investigate alterations in several neurocognitive systems. These include threat processing, reward processing, emotion regulation, and executive control. Below I will provide a brief overview of these systems, their role in the development of psychopathology, and examples of studies that explored them in maltreated children and adolescent.

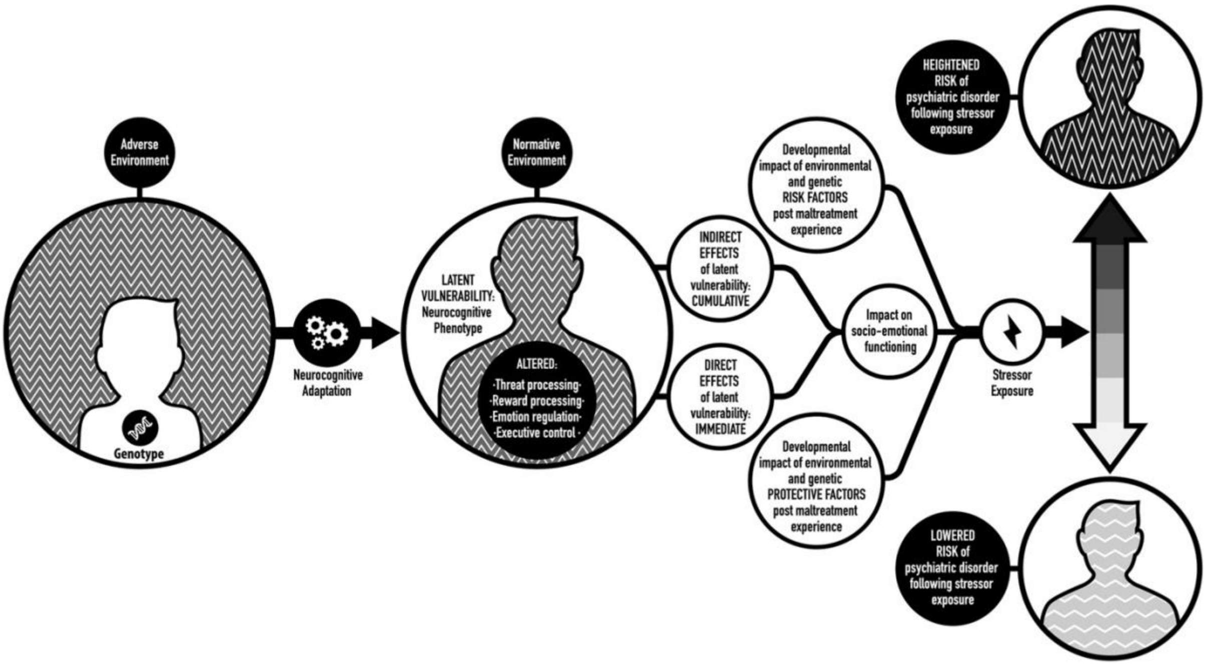


Figure 1. A visual representation of latent vulnerability at the neurocognitive level. Outcomes associated with psychopathology based on risk, protective factors, and genotypes. Reprinted with permission from McCrory et al. (2017).

1.7.1 Markers of latent vulnerability

1.7.1.1 Threat processing

One of the systems where research found evidence of latent vulnerability is threat processing, which refers to the ability to identify and react to negative, possibly dangerous stimuli. As this ability is essential for ensuring survival, substantial neurobiological and cognitive resources are allocated to it (Öhman, 2009), and alterations in this system mean that individuals may be at a higher risk of developing maladaptive behaviours, such as hypervigilance and/or avoidance, usually linked to anxiety disorders (Wald et al., 2013). This is because these coping mechanisms may impair functioning by taking away resources from other important systems (Rogosch et al., 2011). Substantial research shows that exposure to institutionalization and maltreatment alters the neural activity of the threat system, even in children free of psychopathology (Maheu et al., 2010; McCrory et al., 2011, 2013). Research involving both humans and animals indicates that the amygdala is crucially involved in recognizing salient stimuli, especially those linked to threats or dangers (Phelps & LeDoux, 2005). A review and quantitative meta-analysis by (Hein & Monk, 2017) comprising 20 studies, and 1,733 participants shows that maltreatment is associated with increased bilateral amygdala activation to emotional faces. Furthermore, the amygdala maintains interconnected relationships with adjacent subcortical temporal regions related to fear conditioning, such as the hippocampus, as well as with cortical regions engaged in regulatory responses and salience detection. These cortical areas include the anterior insula, the dorsal anterior cingulate cortex (dACC), and ventromedial prefrontal regions (Shin & Liberzon, 2010). For example, the meta-analysis by (Hein & Monk, 2017) also showed an increased activation in the parahippocampal gyrus and insula. A study by (McCrory et al., 2011) investigating threat processing in children exposed to maltreatment in community settings (N=20), found that the maltreated group exhibited higher activation in the amygdala and anterior insula when viewing angry as opposed to neutral faces. Moreover, a later study by the same group (McCrory et al., 2013) showed that the same effect is observed even when these stimuli are presented outside conscious awareness, using a dot probe paradigm. This highlights that altered neural responses to threat are not subject to conscious regulatory influence. On the other hand, a study by (Puetz et al., 2016) found that when maltreated children were asked to name the colour of threatening words (i.e., Stroop task), they exhibited *reduced* activation in the amygdala, insula, ventrolateral prefrontal cortex and orbitofrontal cortex. This pattern was also observed in individuals with PTSD, which may suggest a tendency to dissociate/an avoidant coping style.

1.7.1.2 Reward processing

Relatedly, another system that plays a crucial role for ensuring appropriate adaptation to the environment, is reward processing. Rewards have the purpose of motivating and reinforcing goal-oriented behaviour, and neurological alterations in this system, particularly reduced activation in the striatum, have been linked to the emergence of several disorders, such as depression (Olino et al., 2014), substance abuse (Balodis & Potenza, 2015), and anxiety (White et al., 2017). It has been suggested that heightened reactivity to threats, coupled with reduced responses to rewards (Teicher & Samson, 2016), could signify an adaptive adjustment favouring avoidance in scenarios involving approach-avoidance conflicts. This adaptation could enhance survival prospects in dangerous environments, but also amplify vulnerability to depression (Olino et al., 2014), anxiety (White et al., 2017) and addiction (Balodis & Potenza, 2015) long term. An alternative explanation could be that maltreated children and adolescents are exposed to an environment offering few, unpredictable rewards, leading to decreased anticipation in response to such incentives as a learned behavioural pattern (McCrory et al., 2017). For example, a recent longitudinal fMRI study on adolescents (n = 1576) revealed that reduced striatal response to reward anticipation predicted future clinical depression and anhedonia in a dose-dependent manner. Moreover, diminished activation in the ventral striatum also predicted the emergence of these conditions after 2 years, even in initially healthy individuals (Stringaris et al., 2015). Similarly, studies examining reward processing in community-exposed maltreatment survivors showed that healthy adolescents (N = 106) with self-reported neglect at two different time points correlated with diminished striatal reactivity during reward processing using a monetary incentive delay task (Hanson et al., 2015). Crucially, this effect was observed irrespective of their clinical status.

1.7.1.3 Emotion regulation

In addition to appropriate appraisal of threats and rewards, successful navigation of different environments entails the ability to change our emotional state accordingly, including its valence, duration, and/or intensity (Eisenberg & Spinrad, 2004; Ochsner et al., 2004). To achieve this, one needs to master various mechanisms and strategies, such as cognitive reappraisal, suppression, and attention modulation (Koenigsberg et al., 2010). Alterations in emotion regulation are not only linked to psychopathology, but substantial research on maltreated children shows that changes in this domain could serve as a predisposing factor for the later development of psychiatric disorders and challenges in social functioning (Keenan, 2000). Studies showed that functional and structural alterations are present in several brain regions involved in emotion regulation, such the ventral ACC, lPFC, and the amygdala. (Gee et al., 2013), for instance, presented institutionalized children and adolescents with emotional faces to examine functional coupling between the amygdala and the mPFC, and found that institutionalized young children exhibited more negative connectivity compared to controls. Similarly, in a cohort of typically developing adolescents (N = 31), (S. W. Lee et al., 2015) discovered a positive association between self-reported verbal abuse and current depression symptoms, with more negative functional connectivity observed between amygdala and the rostral ACC. However, another study showed that children exposed to trauma did not show this pattern of negative connectivity between the amygdala and the vACC (Marusak et al., 2015). Similarly, some studies showed increased activity in the dorsolateral PFC, and dorsal and ventral ACC (Marusak et al., 2015; McLaughlin, Peverill, et al., 2015), whereas others found reduced activity in these regions when maltreated children processed social rejection information (Puetz et al., 2016). Taken together, these findings suggest that although evidence points towards an association between maltreatment and functional alterations in brain regions implicated in emotion regulation, the direction of these findings is not yet well understood.

1.7.1.4 Executive control

Planning, flexible thinking, and outcome anticipation are all functions essential for reaching both short-term and long-term goals of emotion regulation (Snyder et al., 2015). These functions have the role of facilitating decision-making and adaptive behaviours, encompassing self-regulation, performance monitoring, and error detection (McCrory et al., 2017).

Alterations in executive control are linked to rumination, and reduced social skills, both of which are predictors of psychopathology (Snyder et al., 2015). Findings from functional MRI studies (Lim et al., 2015; Mueller et al., 2010) show that maltreated children exhibit increased activity in medial (e.g., dACC) and lateral frontal regions (e.g., lPFC) during error monitoring and inhibition, which suggests altered executive control following maltreatment. However, in an important longitudinal study, (Danese et al., 2017) showed that deficits in executive control were explained by pre-existing cognitive deficits prior to maltreatment, as well as SES.

Taken together, these findings show an association between maltreatment and alterations in several neurocognitive systems that may indicate latent vulnerability to future psychopathology. In line with the theoretical framework, these alterations are detected within higher order systems, and, importantly, *before* various forms of psychopathology emerge (McCrory et al., 2017). However, it is also evident that much more work is needed before we can draw firm conclusions about the underlying mechanisms, and that investigation of other neurocognitive (sub)domains, such as emotion recognition and learning would be beneficial. In doing so, we would be able to explore how childhood maltreatment may increase the risk of poor mental health, as well as identifying unique profiles that may not necessarily be associated with risk, but with adaptive functioning despite those adversities.

1.8 Resilience. Conceptualizations and measures

An important stipulation of the theory of latent vulnerability is that alterations carry a probabilistic, rather than a deterministic risk of psychopathology. Indeed, as mentioned above, indicators of latent vulnerability do not predict *when* a psychiatric condition may emerge, and crucially, under certain circumstances, these may also never develop (Yoon et al., 2021). Although researchers do not yet agree on the precise definition of resilience (from the Latin verb “resilire”, to leap back), this is generally described as the ability to achieve positive adaptation despite experiences of adversity. To date, resilience has been conceptualised in three different ways: as a trait/individual feature, as a process, and as an outcome.

Trait-resilience studies have generally focused on identifying personal characteristics that might protect individuals against negative mental health outcomes, using scales such as the Connor-Davidson Resilience Scale (CD-RISC; (Connor & Davidson, 2003)) or the Resilience Scale for Adults (RSA; (Friborg et al., 2005). For instance, a meta-analysis (N studies = 60) by (Hu et al., 2015) investigating the relationship between trait resilience and mental health showed that age and gender moderated the relationship between trait resilience and negative markers of mental health. Specifically, adults showed stronger associations between trait resilience and negative mental health indicators compared to children and adolescents, and this association was stronger in females, suggesting that more attention should be given to them when studying trait resilience and interventions. Similarly, in a prospective longitudinal study by (Pargas et al., 2010), it was found that high child IQ, as well as low levels of perceived maternal control acted as protective factors against depression. In addition, high maternal warmth, high self-esteem, and healthy social functioning all predicted resilient functioning in young adults, irrespective of their mother's status of depression (Pargas et al., 2010).

On the other hand, studies that focused on *resilience as a process* contradict the notion that resilience can be measured directly. Rather, this line of work suggests that it can only be observed in the aftermath of adverse experiences, via a dynamic adaptation over time (Luthar & Zelazo, 2003). That is, adaptive functioning is seen because of complex interactions between individual traits and the environment, which can fluctuate throughout the life span (Stainton et al., 2019). Importantly, these fluctuations can also take place within a single individual, depending on environmental circumstances, and as a function of time (Luthar, Cicchetti, & Becker, 2000). This means that, for instance, an individual can function well in the academic domain, yet still struggle socially or emotionally, and experience the reverse pattern at a different point in time. Relatedly, recent studies have opted for a multilevel approach using dimensional rather than categorial measures of resilience (Kalisch et al., 2017; Southwick et al., 2014). For instance, in a study by (Cornwell et al., 2023) resilience was operationalised by regressing different adversity types (e.g., maltreatment, crime exposure) against multiple forms of psychopathology (e.g., CD, ODD, anxiety), and calculating individual deviations from the expected positive relationship between adversity and psychopathology. Then, Cornwell and colleagues assessed whether these continuous resilience scores would be related to whole brain grey matter volume (GMV) alterations, using structural MRI from the FemNAT-CD study. Results showed that resilience was positively correlated with GMV in the right inferior frontal and medial frontal gyri. Moreover, interactive sex effects were also observed, such that resilience scored positively correlated with GMV in the left temporal gyrus in males, but negatively correlated with GMV in females for this area (Cornwell et al., 2023).

Resilience has also been conceptualised *as an outcome*, with studies focusing on different developmental domains of functioning, such as behavioural, emotional, social, and academic competence. A comprehensive review by (Walsh et al., 2010) showed that for indicators of emotional and behavioural competence, one of the most commonly used measure is the Child Behaviour Checklist (CBCL; (Achenbach & Ruffle, 2000)), which generates an overall score for behaviour problems, distinct scores for externalizing and internalizing behaviours, as well as various specific symptom scales, such as thought problems, withdrawal, somatic complaints, and rule-breaking behaviour. Other researchers, however, used indicators of specific disorders, such as Children's Depression Inventory (CDI), or the Trauma Symptoms Checklist (TSCC; (Briere, 2011). Importantly, a systematic review by (Meng et al., 2018) showed that from the literature investigating resilience as an outcome, more than 50% of studies explored resilience following childhood maltreatment as the *absence of psychopathology*. These included a wide range of psychiatric disorders, such as depression, anxiety, PTSD, psychosis, or internalizing and externalizing problems (Callaghan et al., 2019; De Bellis et al., 2015; Meng et al., 2018).

In this thesis, resilience was conceptualised by drawing from both outcome and process focused resilience literature. In line with the concept of resilience as an outcome, the analyses included a group of youth with experiences of maltreatment and absence of psychopathology. However, instead of using a narrow definition of resilience such as the absence of PTSD following maltreatment (Morey et al., 2016), maltreated youth were classed as resilient if they also demonstrated absence of *any* other psychiatric diagnoses. This choice was motivated by evidence from prospective longitudinal studies showing that CM increases the risk of multiple forms of psychopathology (Bauer et al., 2022), and that many maltreated youth without PTSD exhibit more symptoms of anxiety and depression compared to those with a PTSD diagnosis (Kiser et al., 1993). Moreover, drawing from research emphasizing the dynamic nature of resilience, this thesis also investigated detectable alterations following maltreatment, which may enhance our understanding of factors associated with resilience. The dynamic, complex nature of resilience was also emphasised by exploring those alterations across multiple domains. This approach was in line with evidence showing that different neurocognitive patterns can be present within an individual (Luthar et al., 2000), whereby a maltreated child can exhibit alterations in one domain (e.g., emotion recognition), but not in another (e.g., emotion learning).

In summary, resilience has been approached through trait, process, and outcome perspectives. Trait-resilience studies highlight protective traits, while process-focused research examines dynamic adaptation. Resilience as an outcome explores diverse domains of functioning, often investigating the absence of psychopathology following childhood maltreatment. Despite these differences in conceptualizations, these definitions provide a comprehensive understanding of resilience and its intricate dynamics and align in their emphasis on three key factors: the existence of adversity or risk for mental illness, the impact of overriding protective factors, and ultimately achieving a more positive outcome than anticipated given the prevailing risk. These attributes are all embedded in the conceptualisation of resilience explored in this thesis.

1.8.1 Prevalence of resilience

Given the heterogeneity in operationalising resilience, it is not surprising that estimates of prevalence of resilience following childhood maltreatment also vary, with ranges between 0 to 20% (Yoon et al., 2019). For instance, dichotomising competence as high (top 1/3) and low functioning (bottom ¾) in each domain described above and using composite scores of overall functioning to further divide children in resilient, middle, and low functioning groups, it was found that 9-18% of the maltreated children were classified as resilient (Flores et al., 2005). Another longitudinal study, however, showed that when followed up across 3 years, only 1.5 % of the maltreated children exhibited competence scores indicative of resilience (Cicchetti & Rogosch, 1997b). Moreover, maltreated children exhibited more declines in functioning (12%) compared to non-maltreated children (9%). Herrenkohl et al. (1991) used the top and bottom 40% scores on emotional, social, and academic domains to divide children into high and low functioning groups and found that 13% of the maltreated children demonstrated resilience. Yet another study by Bolger and Patterson (2003), investigated how many maltreated children performed 1 SD above the mean in one domain compared to a normative cohort, without performing 1 SD *below* the mean in any of the other domains, and found that 9% showed resilience in any of the 4 years of study, but that only 0.9% maintained positive functioning over the 4 years.

1.8.2 Protective factors following maltreatment

To offer further theoretical context for the research questions of this thesis, I will now provide a concise review of protective factors associated with resilience following maltreatment. Fortunately, not all maltreated children experience the negative consequences of this adversity, which suggests that some may display higher levels of resilience. Similar to risk factors, the characteristics that have been shown to contribute to resilient functioning span across individual, interpersonal, community, and societal levels. A large body of research investigating individual-level factors associated with positive adaptation following maltreatment show that certain characteristics, such as self-regulation skills, social competence, and self-esteem significantly contribute to positive outcomes following this adversity (Meng et al., 2018; Yoon et al., 2021). For instance, a longitudinal study by (Oshri et al., 2017) showed that maltreated children with high social skills such as cooperation, responsibility and self-control, performed better in school, had more optimistic expectations about the future, and were less likely to engage in delinquent behaviours and substance use in adolescence compared to maltreated children with lower social skills. Similarly, maltreated children with early self-regulation skills, which involve the ability to control emotional and behavioural response following stressful situations, were more likely to demonstrate positive social and emotional development (Sattler & Font, 2018).

At interpersonal level, most studies have focused on caregivers' social support (i.e., from romantic partners, family, and friends). Substantial research shows that harsh parenting can be transmitted across generations, such that maltreated parents are more likely to abuse or neglect their own children (Conger et al., 2013; Minnis, 2023; Schofield et al., 2013; Thornberry et al., 2013), but that a supportive relationship with a romantic partner can prevent this continuation of maltreatment (Schofield et al., 2013; Thornberry et al., 2013). In addition, a populations based study showed that emotional support from a friend was linked to reduced frequency of physical abuse (Price-Wolf, 2015), and so was family support (Martin et al., 2012). In addition to social support from family and friends, literature suggests that increased community access to health, social, and educational services also act as protective factors against maltreatment. Specifically, proximity to and higher density of mental health and substance abuse, adoption, and parenting issues services, as well as neighbourhoods with higher percentages of child care spaces, were shown to be associated with lower rates of maltreatment (Freisthler, 2013; Klein, 2011; Maguire-Jack & Klein, 2015; Morton, 2013). In addition, neighbourhoods with a higher social cohesion, intergenerational closure, and reciprocated exchange have also shown to be associated with reduce physical abuse (Freisthler & Maguire-Jack, 2015; Molnar et al., 2016).

Similar to societal risk factors, studies have examined protective social and economic policies on maltreatment. Paid family leave, earned income tax credits and benefits, and increases in minimum wages were all found to be associated with decreases in CPS investigations of maltreatment (Klevens et al., 2016; Klevens & Ports, 2017). Importantly, and consistent with evidence from studies on family risk factors, these studies suggest that even small policy-induced increases in family income can lead to population-wide reductions in maltreatment, emphasizing that prevention does not require drastic changes. However, the presence of these protective factors does not guarantee immunity from maltreatment but can increase a child's resilience and reduce the likelihood of negative outcomes.

Taken together, these studies show that childhood maltreatment is a multifaceted public health concern, influenced by various risk and protective factors at different levels of the socioecological model. Finally, it is essential to note that these factors can accumulate and interconnect, influencing the probability of a child experiencing maltreatment. This means that designing and implementing effective prevention strategies becomes a complex task due to the intricate nature of these interactions (Bronfenbrenner, 1977).

1.8.3 Gene x environment interactions

A substantial body of research shows that differences in resilient functioning are heritable, these being approximately 50% attributed to genes (Amstadter et al., 2014). Genes play a crucial role in shaping our neuroendocrine and immune systems, contributing to brain structure and function following childhood maltreatment. For instance, various studies have found gene x environment interactions, whereby the serotonin-transporter linked polymorphic region (5-HTTPLR) (Frodl et al., 2010), neuropeptide-Y (NPY) gene polymorphism rs16147 (Opmeer et al., 2014), monoamine oxidase A (MAOA) gene (Kim-Cohen et al., 2006) or the FK506 binding protein 5 (FKBP5) gene (Klengel et al., 2013). However, a recent meta-analysis (N studies =31) found no support for a maltreatment × 5-HTTLPR interaction, although maltreatment had a main effect on risk for depression (Culverhouse et al., 2018). As discussed in section 1.6, positive environmental factors at individual, family, and societal level all play a key role in promoting resilient functioning (Cicchetti, 2013; Fritz et al., 2018). Family support in adolescence, friendship interactions (Van Harmelen et al., 2016), earlier age of adoption or foster care (Olsavsky et al., 2013), have been shown to support resilient functioning by influencing core neurobiological processes such as cytokines, HPA axis, as well as brain structure and function.

Taken together, these findings suggest that the ability to function well after childhood maltreatment is influenced by the complex interplay of genetic, and social factors. Genetic influences account for about 50% of differences in resilience, with gene-environment (e.g., social support) interactions playing an important role in resilient functioning.

1.9 Resilience and latent vulnerability across modalities

In line with the multifaceted dynamics underlining both latent vulnerability and resilience following childhood maltreatment, this thesis focuses on identifying multimodal, latent vulnerability markers, and protective factors that may contribute to resilience. Specifically, I aimed to explore neurocognitive and neurobiological markers in maltreated children and adolescents in the following domains: emotion recognition and learning, autonomic nervous system functioning, and brain structure. Below I will introduce these domains (which are explored in depth in Chapter 3, 4 and 5), and highlight important inconsistencies in findings. Then I will discuss the role of co-occurring psychopathology and sex differences, which I suggest play a crucial role in explaining those discrepancies.

1.9.1 Emotion processing: Emotion recognition and learning

To advance our understanding of latent vulnerability and resilience following maltreatment, it has been suggested that attention should be shifted towards "observable" markers of affective responses to social situations (Collishaw et al., 2016; Luke & Banerjee, 2013). Childhood maltreatment has been associated with deficiencies in social cognition, including recognition of facial emotion expressions and emotion learning (Gallese et al., 2004) (Chapter 3). Facial expression recognition entails the ability to use partial information derived from the dynamic modulation of facial movements to formulate a hypothesis about the underlying emotion being conveyed (Pollak & Sinha, 2002). This emotion is then categorized, contributing to the anticipation and prediction of potential behavioural responses from other individuals (Pollak & Sinha, 2002). Swift and accurate identification of emotions is thus of paramount importance for child development, and it has been suggested that children modify their perceptual mechanisms to prioritize processing prominent and familiar characteristics within their surroundings because of their exposure to social interactions. Following childhood maltreatment, these sensory thresholds can be altered, resulting in reduced efficiency in managing, interpreting, and identifying emotions (Pollak et al., 2000, 2005). However, one important limitation in the current literature is that findings vary significantly when it comes to pinpointing the particular emotions that maltreated youth might struggle to identify. (da Silva Ferreira et al., 2014). That is, some studies report that maltreated children are impaired in global facial expression recognition (Luke & Banerjee, 2013), others suggest specific impairments in recognizing negative emotions (Leist & Dadds, 2009; Pajer et al., 2010; Shackman & Pollak, 2005), whereas a recent meta-analysis exploring the association between adversity and facial expression recognition in youth found reduced recognition for fear and happiness (Saarinen et al., 2021).

Similarly, maltreatment has also been shown to alter emotion learning (i.e., the ability to learn from positive and negative feedback (Schoenbaum & Roesch, 2005). Studies from both animals and humans show an association between adversity and stimulus-reinforcement learning, especially reward-based learning (Novick et al., 2018). That is, it was found that youth with adverse life events perform worse in reward-incentive tasks, and are slower at learning from both positive and negative stimuli-response associations (Dennison et al., 2019a; Harms et al., 2018; Kasparek et al., 2020).

1.9.2 Autonomic Nervous System (ANS) functioning

In Chapter 4, I explored potential markers of latent vulnerability and resilience following maltreatment in autonomic nervous system (ANS) functioning. The ANS controls an organism's reaction to environmental shifts that demand adjustment, being critical in the stress response. This is further divided into the sympathetic (SNS) and parasympathetic nervous systems (PNS). In the SNS, activation takes place as a response to stressors, coordinating the 'fight or flight' reaction. That is, its main aim is to gather resources to appropriately respond to environmental challenges. The PNS, on the other hand, has the role of inhibiting SNS activation, to promote growth and restoration. In the current literature, activation in these two subsystems of the ANS has been measured in several direct and indirect ways. For SNS, studies have used heart rate and blood pressure as indirect measures of SNS response, whereas others have utilized purer/direct measures, such as skin conductance level, or the pre-ejection period (PEP) (i.e., the time between ventricular contraction and blood ejection into the aorta). Thus, strong SNS activity is indicated by faster heart rate, raised blood pressure, increased skin conductance level, and *shorter* PEP at baseline and in response to challenge. For PNS, most research to date has focused on respiratory sinus arrhythmia (RSA), the high frequency component of heart rate variability (HRV). This refers to the coupling of heart rate and respiration, that leads to variability in heart rate during inhalation compared to exhalation.

According to the Neurovisceral Integration Model, high HRV suggests a healthy, adaptive PNS system, while low HRV indicates compromised PNS function (Kemp et al., 2017). A typical stress response involves activating the ANS, then triggering the HPA axis, which produces cortisol, and finally deactivating the ANS. This well-timed process enables individuals to handle threats and return to normal functioning afterwards. Abnormal stress responses, on the other hand, include extended hyperresponsivity or hypo-responsivity, both of which can lead to an inability to adaptively address stressors. These responses can have lasting negative effects on emotional and cognitive well-being, and contribute to the development and persistence of psychopathology (Graziano & Derefinko, 2013). While existing research predominantly focused on the association between childhood maltreatment and HPA axis dysregulation, the role of the ANS has received less attention (Young-Southward, Svelnys, et al., 2020). While some studies show that disruptions in ANS functioning may mediate the association between maltreatment and psychopathology, less is known about the potential links between specific SNS and PNS activity and psychopathology (Young-Southward, Svelnys, et al., 2020).

1.9.2.1 Sympathetic Nervous System (SNS) functioning

For SNS, available studies on cardiovascular response (i.e., indirect measure of SNS activity) in maltreated children are mixed. For instance, a study by (Carrey et al., 1995) investigated the physiological reactions of children aged 7-13 who had experienced physical or sexual abuse, and showed that abused children had significantly lower baseline pulse height and smaller pulse height changes during test conditions, in contrast to the non-abused children. Similarly, (Pollak et al., 2005) conducted a study on physically abused children aged 4-5, who were given a task while listening to a conflict conversation with instances of ongoing anger in the background. It was found that in response to the active anger, unresolved anger, and resolution periods, physically abused children displayed a slower heart rate compared to their baseline, a pattern that was interpreted by the authors as a sign of heightened attentional arousal during these different emotional phases. In contrast to these findings, however, in a study by (Koopman et al., 2004), maltreated adolescents aged 11-16 from a juvenile probation centre were subjected to both stressful and non-stressful interviews. Their findings suggested that maltreated adolescents with higher scores on the childhood trauma interview, exhibited a faster average heart rate during both types of interviews compared to those with lower trauma scores. Moreover, a longitudinal study by (MacMillan et al., 2009) showed that maltreated girls aged 12-16 years did not significantly differ in baseline or responsiveness of heart rate after a social stress task compared to non-maltreated girls.

Similarly, studies that focused on more direct measures of SNS activity (N=5), such as PEP and EDA, are also inconsistent. A study by (McLaughlin, Sheridan, Alves, et al., 2014), examining cardiac output in maltreated adolescents aged 13-17, indicated that exposure to maltreatment was associated with reduced PEP responsivity during the math segment of the stress task, reflected by a smaller decrease from the baseline. (McLaughlin et al., 2016a) presented maltreated and non-maltreated children aged 6-18 with a fear conditioning task, and found that during conditioning, maltreated children displayed a diminished skin conductance response (SCR) to the conditioned stimulus compared to controls. However, (Ben-Amitay et al., 2016) found no significant association between different types of abuse and SCR when children viewed negative stimuli (e.g., snake, girl crying, covering her face).

1.9.2.2 Parasympathetic Nervous System (PNS) functioning

For PNS, the literature is even more limited, with only three studies having examined RSA in maltreated individuals. These results are also mixed, and not easily comparable. Using an adapted version of the strange situation task with foster caregivers, (Oosterman et al., 2010) showed that maltreated children aged 2-7 years exhibited smaller decreases in RSA from baseline to separation, and increased RSA on reunion, compared to non-maltreated children. (Shenk et al., 2010) studied physiological responses in sexually abused and non-abused 18-year-old females to a timed mental rotation task. Those findings suggested that sexually abused females displayed an unusual physiological reaction, marked by reduced RSA and a weakened cortisol response. Finally, a more recent study by (Lunkenheimer et al., 2019) explored the association between mother-child RSA and interactive repair during puzzle tasks in maltreating and non-maltreating pairs. They found that in maltreating pairs, low levels of mother-initiated repair were linked to an increase in child RSA, while non-maltreating pairs showed a decrease in child RSA during interactive repair.

1.9.3 Brain structure – Alterations in cortical and subcortical volume

Finally, the last domain in which I explored neurobiological markers of latent vulnerability/resilience in maltreated children is brain structure, specifically volume (Chapter 5). Literature suggests that neurobiology changes in the brain might also underlie psychopathology following maltreatment. Indeed, recent research indicates that early-life adversities can modify the course of neurodevelopment, impacting sensory systems, network architecture, and neural circuits. These findings come from observed changes in neurons, glial cells, dendrites, synapses, myelination, and the activity of neurotransmitters and growth factors (Teicher et al., 2016b). Modern neuroimaging techniques, such as magnetic resonance imaging (MRI), have enabled researchers to study non-invasively these neurobiological alterations in individuals exposed to childhood maltreatment. Using techniques like surface-based morphometry (SBM) and voxel-based morphometry (VBM), it has been possible to investigate microstructural abnormalities such as cortical thickness and volume. Cortical thickness refers to the distance between the outer surface of the brain's cerebral cortex and an inner boundary, typically the white matter, and it is considered a heritable and stable structural brain feature (Panizzon et al., 2009). Cortical and subcortical volume, on the other hand, refer to the amount of grey matter/tissue in the cerebral cortex, and in regions that lie beneath the cerebral cortex, respectively. As opposed to cortical thickness, grey matter volume (GMV) is thought to be less influenced by genetic factors, and more susceptible to early life experiences, such as childhood maltreatment (Lim et al., 2014). The majority of studies investigating GMV alterations in maltreated individuals have focused on specific regions of interest (ROI) implicated in memory processing, emotion regulation, and executive control. These include the prefrontal cortex (PFC), hippocampus, anterior cingulate cortex (ACC), and the amygdala (Paquola et al., 2016), whereas others have opted for a whole brain approach, exploring volume alterations globally (Hakamata et al., 2022). Importantly, these alterations in brain morphology can become apparent even in individuals without psychopathology.

In line with studies on emotion processing and ANS functioning in maltreated youth, current neuroimaging studies investigating volume alterations associated with childhood maltreatment are inconsistent. One meta-analysis suggested that individuals who experienced childhood maltreatment display reduced GMV in specific brain areas such as the orbitofrontal cortex (OFC), the limbic-temporal regions, the inferior frontal cortex, and the left sensorimotor cortex (Lim et al., 2014). These regions are implicated in affect and cognitive control, and sensory functions, respectively. Other studies indicated reduced volume in the right dorsolateral PFC and right hippocampus (Paquola et al., 2016). On the other hand, (Carrion et al., 2009) showed that maltreated individuals with PTSD showed *increased* GMV volume in the PFC, and smaller GMV in the pons and posterior vermis areas. Similarly, childhood maltreatment has also been found to be associated with *larger* left hippocampal volume, and slower hippocampus development over time, as a function of psychopathology (Whittle et al., 2013). The most recent meta-analysis by (W. Yang et al., 2023) suggests that childhood maltreatment is associated with volume reductions in the median cingulate/paracingulate gyri and the left supplementary motor area (SMA). Moreover, results from structural MRI studies that focused on resilience specifically, and accounted for the presence of psychopathology, are also mixed. A review by (Eaton et al., 2022) shows that these studies are highly heterogeneous; (Burt et al., 2016) found that adolescents exposed to early life adversities, but without psychopathology (i.e., resilient) had *increased* volume in the right middle frontal and right superior frontal regions compared to non-maltreated and maltreated with psychopathology adolescents, respectively. Similarly, (De Bellis et al., 2015) found that maltreated youth without PTSD exhibited *increased* cerebral and cerebellar volume compared to maltreated youth with PTSD. However, (Barzilay et al., 2020) found that adversity without psychopathology was associated with reduced total brain volume compared to those who experienced adversity and exhibited psychopathological symptoms.

1.9.4 The role of co-occurring psychopathology

As mentioned in section 1.9.3, one important limitation in understanding how maltreatment relates to these domains, which might explain inconsistent findings, is the high co-morbidity with psychopathology. Substantial research indicates that childhood maltreatment is associated with both internalizing and externalizing psychopathologies, which are themselves associated with alterations in emotion recognition, learning, ANS functioning, and brain volume. Alterations in emotion recognition are related to various psychiatric disorders, such borderline personality disorder (BPD) (Porter et al., 2020), and psychosis (Varese et al., 2012). These findings raise the question of whether altered recognition of emotions from facial expressions are related to childhood maltreatment, or associated with psychopathology (Teicher et al., 2016a). To date, very few behavioural studies have explored maltreatment and psychopathology effects on emotion recognition in the same individual (Saarinen et al., 2021), making it difficult to understand how those variables relate to each other. Similarly, for emotion learning, the few studies available suggest that presence of psychopathology did not influence reward learning responses in maltreated youth, yet those samples are also high in co-morbid psychopathology (Dennison et al., 2019b; Kasparek et al., 2020; Mueller et al., 2010). Likewise, ANS dysregulation has extensively been associated with psychopathology. Specifically, for SNS, meta-analyses show that low resting and stress reactivity EDA are associated with conduct problems, psychopathy, (de Looff et al., 2022), and depression (Sarchiapone et al., 2018). For PNS, studies show that low resting and reactive RSA are also associated with several internalising and externalising psychopathologies and syndromes, such as anxiety, phobias, and autism spectrum disorder (Beauchaine, 2015). Moreover, a meta-analysis by (Sigrist et al., 2021) exploring the association between maltreatment and resting HRV found that when samples came from clinical populations, where psychopathology was present, maltreatment was associated with lower HRV. Finally, this notable overlap between maltreatment and psychopathology is also present in studies investigating brain structure (W. Yang et al., 2023). GMV deficits have been associated with many specific psychiatric disorders, such as schizophrenia, bipolar disorder, OCD, and anxiety (Goodkind et al., 2015), as well as general psychopathology (Durham et al., 2021). In line with studies on ANS functioning, a recent meta-analysis by (W. Yang et al., 2023) exploring the association between adversity and brain structure in adults showed that many studies investigated maltreated groups with co-morbid psychopathology that they did not account for. Thus, given this literature, it is possible that inconsistencies in findings related to emotion recognition, emotion learning, ANS functioning, and brain volume may be partly due to co-morbid psychopathology.

1.9.5 Sex matters

In addition to psychopathology (and other specific factors discussed in detail in each empirical chapter), sex differences might also influence how maltreatment is related to emotion recognition, emotion learning, ANS indices, and brain structure. Indeed, a large body of literature suggests that males and females respond differently to stress (Bangasser & Wiersielis, 2018; Kudielka & Kirschbaum, 2005). With regards to emotion recognition, studies showed that females outperform males (Thompson & Voyer, 2014), and that the type of emotion influences the magnitude of these sex effects, with females exhibiting an advantage in recognizing negative emotions (e.g., anger, sadness, fear, disgust). For emotion learning, however, studies show that males are better than females (Evans & Hampson, 2015). Moreover, males and females are also different in their PNS and SNS activation. Females are shown to exhibit higher PNS activity at rest (Koenig & Thayer, 2016), and higher SNS activity both at rest and in response to stress, compared to males (Bari, 2020). Finally, brain structure is also sex dependent. Females have generally smaller GMV compared to males (Gennatas et al., 2017), and males have also been found to exhibit larger volume in specific regions such as the amygdala, thalamus, or the putamen (Koolschijn & Crone, 2013; S. Yang et al., 2017).

In the context of maltreatment, however, it is unclear how sex may influence these domains. Sex should be a key factor to investigate, given that it is associated with both the type and the severity of psychopathological symptoms. For instance, it is now widely accepted that females are more likely to develop internalizing psychopathologies (e.g., depression, anxiety), whereas males show a greater prevalence of externalizing psychopathologies, and early onset neuropsychiatric disorders, such as autism, attention deficit disorder with hyperactivity (ADHD), or dyslexia (Rutter et al., 2003). Despite this, sex differences in emotion recognition, learning and ANS functioning in maltreated youth is not well understood, and studies examining sex differences in brain structure in maltreated individuals are inconsistent. For instance, one meta-analysis found that maltreated females have smaller GMV compared to maltreated males (Paquola et al., 2016), whereas another found no significant sex differences on GMV in maltreated youth (Lim et al., 2014). Moreover, (De Bellis & Keshavan, 2003) found that maltreated boys with PTSD exhibited reduced cerebellar and increased lateral ventricular volume compared to maltreated girls with PTSD diagnoses. However, as discussed above, it is difficult to know whether these findings reflect an association with maltreatment, with PTSD diagnoses, or both.

1.9.6 Summary

In summary, experiences of emotional, physical, and sexual abuse, and emotional and physical neglect in childhood represent important risk factors for a variety of mental and physical health outcomes. These experiences have a prevalence ranging from 36% to 0.4%, depending on sex, subtype of maltreatment, and the type of informant (e.g., self-reports versus official records), with official records suggesting underrepresentation. Measures of maltreatment also vary; retrospective measures generally provide a comprehensive overview of a person's experiences but can be biased. Prospective measures, on the other hand, provide detailed, real-time information about the development of these experiences, but are limited to specific time periods. Maltreatment has also been shown to be associated with a plethora of risk factors, at individual, interpersonal, community, and societal levels. Research also shows that abuse and neglect impact individuals' cognition, social and behavioural function, and mental and physical health. Theoretically, it has been proposed that maltreatment leads to neurobiological abnormalities across systems (e.g., immune, endocrine, cardiovascular, central nervous system), and that prolonged efforts of adaptation can lead to allostatic load, increasing risk for psychopathology. A more recent theory proposed by McCrory and colleagues focuses on the detectability of these alterations across systems, which are thought to have adaptive value in adverse environments but are maladaptive long-term. Importantly, this theory stipulates that alterations become apparent before psychopathology emerges, thus carrying important implications for prevention strategies. Evidence in support of this theory comes from studies showing alterations following maltreatment in threat and reward processing, emotion regulation, and executive control.

Importantly, however, not everyone who experiences maltreatment develops a form of psychopathology, and research shows that various factors can act as a buffer against negative mental health outcomes. Like risk factors, these span across individual, interpersonal, community, and societal levels, and are thought to contribute to resilience. This phenomenon has been conceptualised in the literature as a trait, an outcome, and as a process, highlighting its dynamic nature within individuals and as a function of time, being facilitated by complex interplays between genes and environmental factors. Importantly, the prevalence of resilience following maltreatment is very low, ranging from 0 to 20%, depending on operationalization. This suggests that further efforts are needed to identify factors that may enhance adaptive functioning following these adversities. The aim of this thesis was thus to investigate markers of latent vulnerability and resilience across modalities, focusing on emotion recognition and learning, ANS functioning, and brain volume. The main rationale stems from studies generally not accounting for the presence of psychopathology in the maltreated samples, making it difficult to disentangle alterations linked to maltreatment and those associated with psychopathology. Finally, as sexes have been shown to respond differently to stress, this thesis also investigated moderating effects of sex on the associations between maltreatment and psychopathology with emotion processing, ANS system and brain structure.

1.9.7 Thesis outline

The following chapters focus on the methodologies used in each empirical study, and the three areas of investigation that have been either understudied and/or produced mixed findings. These are facial emotion recognition, emotion learning (i.e., reward- and punishment-based learning), ANS functioning (i.e., PNS and SNS activation), and brain volume. Chapter 2 will focus on describing the two datasets used in this thesis – the FemNAT-CD and ABCD study, as well as the methods used in the empirical chapters. These include statistical analyses, psychophysiology measures, and structural magnetic resonance imaging (sMRI). Chapter 3 explores alterations in facial emotion recognition and emotion learning in maltreated youth aged 9-18 from the FemNAT-CD study. Chapter 4 investigates heart rate variability (RSA) and electrodermal activity differences in maltreated youth with and without psychopathology (also from FemNAT-CD) to assess PNS and SNS functioning respectively. Chapter 5 focuses on cortical and subcortical volume in ROIs, as well as in the whole brain, using data from maltreated children in the ABCD study. Finally, in Chapter 6, I discuss findings from these three empirical chapters, focusing on their strengths, limitations, and implications for intervention and future research.

Please note that Chapter 3 has been published in the *European Child and Adolescent Psychiatry* (ECAP) journal (Diaconu et al., 2022). Findings from Chapter 4 have been submitted for publication to the journal *Development and Psychopathology* and have also been presented as a poster at Society of Biological Psychiatry conference in 2023.

Chapter 2

CHAPTER 2: DATASETS AND KEY MEASURES

2.1 Overview

Chapter 2 provides an overview of the two datasets used in Chapter 3 and 4 - The FemNAT-CD project, and Chapter 5 - The Adolescent Brain and Cognitive Development Study (ABCD). As the ABCD study in open-source, and substantial information is readily available on the consortium, I will dedicate more space to the description of the FemNAT-CD project instead. I will also introduce key measures used in this thesis and discuss methodological differences between The FemNAT-CD based and the ABCD-based chapters. For instance, the assessment of maltreatment exposure varied between Chapter 3, 4 and 5, but the same measures were used in all empirical chapters to assess psychopathology.

2.2 The FemNAT-CD Project

2.2.1 Overview and Aims

The data presented in Chapters 3 and 4 have been collected as part of the European Commission's 7th Framework Health program (FP7) project, 'The Neurobiology and Treatment of Adolescent Female Conduct Disorder' (FemNAT-CD; Freitag et al., 2018). This project is a collaboration between 17 sites spanning eight European countries: Germany, Greece, Hungary, Ireland, the Netherlands, Spain, Switzerland, and the United Kingdom. The primary goal of the consortium was to uncover the underlying neurobiological, neurocognitive, and environmental factors contributing to Conduct Disorder (CD), with a specific emphasis on females, as they are often underrepresented in most CD studies (Freitag et al., 2018). Recruitment took place from January 2014 to February 2018, involving a total of 1827 youths. Among them, 880 had CD (61% females), while 947 were typically developing (TD) youths (65% females). The process of data collection encompassed a range of methodologies, including questionnaires, behavioural assessments, neurophysiological and genetic measurements, as well as structural and functional MRI scans. The following sections provide a comprehensive outline of the recruitment and evaluation protocols, as well as a description of key measures used in this thesis.

2.2.2 Recruitment

Recruitment of participants occurred at 12 European sites, drawing from diverse sources such as local clinics, mental health services, youth offending services, mainstream and specialized schools, youth clubs, community services, outreach events, and informal referrals.

2.2.3 Eligibility and exclusion criteria

Females and males aged 9-18 were eligible to take part if they had an IQ of 70 or higher and no current or past indications of conditions such as autism, schizophrenia, genetic syndromes, neurological disorders, or traumatic brain injury. Additionally, typically developing (TD) participants, who did not have Conduct Disorder (CD) or Oppositional Defiant Disorder (ODD), had to have no history of externalizing disorders, bipolar disorder, mania, or any ongoing psychiatric disorders. Individuals were categorized as 'cases' if they a) fulfilled DSM-5 diagnostic criteria for CD, b) were aged 9-12 and met the criteria for ODD with at least one CD symptom, or c) were over 12 and met the criteria for ODD with at least two CD symptoms. Siblings of previous participants were excluded, and all participants were required to bring a parent, guardian, or responsible adult to the initial session as an additional informant.

2.2.4 Consent

Written informed consent was provided by a parent, guardian, or another responsible adult on behalf of minors (below 16 or 18 years depending on the data collection site), while minors themselves provided written assent. Participants above the specified age, along with parents and guardians, offered written informed consent for their own involvement. Collection of all data occurred within six months from the date of obtaining informed consent.

2.2.5 Data collection procedure

Initial referrals to the project underwent a preliminary telephone assessment for suitability. Participants deemed likely to meet eligibility criteria, along with their parents or guardians, were subsequently invited to a more comprehensive screening session conducted either at a local site (such as a university or affiliated clinic) or at the participant's residence. This initial session typically lasted 1-3 hours and began with obtaining informed consent. Trained researchers separately interviewed participants and their parents or guardians to evaluate the presence of any mental disorders, alongside administering an IQ test. Subsequently eligible participants attended a second session lasting approximately two hours, during which they completed questionnaires, provided saliva samples for genotyping, and underwent neurophysiological and neurocognitive assessments. This session also typically covered topics like parenting and facial emotion recognition. For those participating at specific sites, a third testing session lasting around two hours involved collecting MRI data. Following each session, participants received a modest financial reimbursement or equivalent vouchers, in accordance with local ethics committees' approval. Detailed descriptions of the measures used to group participants into maltreated and non-maltreated groups with and without psychopathology throughout Chapter 3, 4, and 5, as well as measures used for included covariates are provided below.

2.2.6 Key measures

2.2.6.1 Children's Bad Experiences Questionnaire (CBE)

In Chapters 3 and 4, consistent with prior work on maltreatment (Caspi et al., 2002), youth were divided into maltreated and non-maltreated groups using the Children's Bad Experiences Questionnaire (CBE), a 5-item semi-structured interview for parents, caregivers, or guardians to provide information about the child's experiences of physical, psychological, and sexual harm. Specifically, the caregivers responded to standardized probe questions aimed at investigating whether the child/adolescent had experienced i) harm on purpose, ii) harm during discipline, iii) sexual harm, or iv) harm that led to the involvement of an agency (e.g., social services). Examples of probe questions included "Do you remember any time when the child was disciplined severely enough that he or she may have been hurt?" or "Has there been any other situation where your child has been harmed by someone (not accidents)?". Following each discussion, interviewers rated privately the probability that the child had been severely harmed (Lansford et al., 2002). For instance, in the case of physical harm, using a criterion of intentional strikes to the child by an adult that left visible marks for more than 24 hours or that required medical attention, a score of 0 was assigned if maltreatment had definitely not or probably not occurred, and a score of 1 was assigned if maltreatment had probably occurred, definitely occurred, or if authorities had been involved (Lansford et al., 2007). Each rater's judgement (i.e., no/probable/definite maltreatment) was compared with scores from a neutral rater and agreement between the independent raters was reported as 90% ($\kappa = 0.56$) in previous studies (Dodge et al., 1995) and in ours.

2.2.6.2 Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version (K-SADS-PL)

The Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version (K-SADS-PL), developed by (Kaufman et al., 1997a), is a semi-structured diagnostic interview employed to evaluate current and past psychopathology in children and adolescents. Trained researchers individually administered the interview to participants and their parents or responsible adult informants, generating combined parent-child summary ratings for all symptoms (past, present, and lifetime). Discrepancies in symptom ratings were resolved through discussions among assessors until a consensus on the summary rating was reached. Except for CD, ODD, and ADHD, where DSM-5 criteria were used, all diagnoses were generated based on the DSM-IV-TR diagnostic criteria, which were current at the outset of the project (APA, 2000). Inter-rater reliability for current CD diagnoses was high (94.7% agreement across raters, Cohen's kappa=0.91).

2.2.6.3 The Child Behaviour Checklist (CBCL)

The Child Behaviour Checklist (CBCL; Achenbach & Ruffle, 2000) constitutes a 120-item assessment designed to evaluate emotional, social, and behavioural issues. This checklist is completed by parents/caregivers to examine eight dimensions: anxiety/depression, withdrawal, somatic complaints, thought problems, attention problems, rule-breaking behavior, and aggressive behavior. Throughout this thesis, I focused on total T scores for overall problems in the main analyses, and composite subscales scores measuring internalizing and externalizing problems in secondary analyses. However, scores for each of the eight dimensions are also provided in each empirical chapter for descriptive purposes.

2.2.6.4 Grouping

Based on the CBE, K-SADS-PL, and CBCL measures, participants were grouped into four mutually exclusive groups as follows: youth with and without maltreatment based on the CBE were divided into groups with high psychopathology if participants had total CBCL T scores > 65 (i.e., the clinical cut off; Mazefsky et al., 2011), *and* presence of at least one psychiatric diagnosis based on K-SADS-PL. Conversely, youth with CBCL T scores < 65 and absence of *any* psychiatric disorder based on the K-SADS were allocated to the low psychopathology group.

2.2.7 Covariates

As outlined in Chapter 1, maltreatment exerts negative effects on cognitive abilities and educational achievements, with these effects often enduring from early childhood to adulthood (Cowell et al., 2015; Danese et al., 2017; Irigaray et al., 2013). Likewise, there is evidence linking pubertal timing (Negriff & Trickett, 2010) and socioeconomic status (SES; (Farrington & Ttofi, 2021; Marcal, 2018) to maltreatment. Importantly, there is also evidence of an association between cognitive abilities (Abramovitch et al., 2021), pubertal status (Negriff & Trickett, 2010), SES (Peverill et al., 2021) and various psychopathological problems. For these reasons, all analyses incorporated these variables as covariates.

2.2.7.1 Wechsler Intelligence Scale (WASI, WAIS, WISC)

Regarding IQ assessment, English-speaking sites employed the vocabulary and matrix reasoning subscales of the WASI-I (Wechsler Adult Intelligence Scale - Fourth Edition, 1999). For other sites, the vocabulary, block design, and matrix reasoning tests of the WISC (Wechsler Intelligence Scale for Children, for participants aged 16 or under) or WAIS (Wechsler Adult Intelligence Scale, for participants aged 17-18 years; Wechsler, 2008) were used.

2.2.7.2 Pubertal Development Scale (PDS)

The Pubertal Development Scale (PDS), developed by Petersen, Crockett, Richards, Maryse, & Boxer in 1988, is a self-report tool for assessing the progression of puberty. It involves items concerning aspects like body and facial hair growth, height, voice changes, and menstruation, which are rated on a scale ranging from 1 ('not yet started') to 4 ('seems complete'). Participants are categorized into stages such as pre-pubertal, early pubertal, mid-pubertal, late pubertal, or post-pubertal. Initially, a response option of 0 ('I don't know') was included, but it was later removed due to its tendency to result in excessive missing data after the start of data collection.

2.2.7.3 Socioeconomic status (SES)

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

Reliability (internal consistency) of the composite SES score was acceptable (Cronbach's Alpha = .74). The reported SES values are comparable with previous large samples derived from the FemNAT-CD consortium.

2.2.8 Imputation of missing data

Statisticians from the Institute of Medical Biometry and Statistics (IMBI), a member of the FemNAT-CD consortium, performed missing data imputation. Initially, missing values for the PDS were imputed separately, preceding the decision to impute missing data for other measures. The description following is a standardized text provided by IMBI for use in all FemNAT-CD consortium publications:

‘Regarding the PDS score, missing values were imputed using the entire FemNAT-CD sample. Recognizing that addressing missing data in a multi-item instrument is best handled by imputing at the item level, a practice substantiated by Eekhout et al. (2014), the approach involved initially imputing missing values for individual items and subsequently calculating scores based on the imputed items. The imputation procedure was executed using the SAS® version 9.4 software with PROC MI, implementing the fully conditional specification (FCS) technique which accommodates flexible specification of multivariate imputation models for diverse missing patterns involving both categorical and continuous variables (Liu & De, 2015). Given the ordinal measurement level of the items, the FCS statement incorporated the logistic regression method. Imputation diagnostics encompassed assessing the distribution of observed and imputed items and scores. Notably, imputation for the PDS items was conducted separately for males and females due to sex-specific items (item 2 for both genders, and items 4, 5a of the female form or items 4, 5 of the male form). The imputation model included variables such as the aforementioned sex specific PDS items, the remaining PDS items (items 1 and 3), age at PDS, age at informed consent (for imputing age at PDS if missing), weight, case/control status, site, and migration status.

For the remaining measures, the same imputation procedure was applied separately. The model included variables like all items of the respective questionnaire, age, IQ, group (case/control), sex (male/female), site, comorbidities (PTSD, ADHD, ODD, depression, anxiety), and items from other questionnaires if correlated with at least one item with a correlation coefficient ≥0.4. For the parent-report Alabama Parenting Questionnaire (APQ; Essau, Sasagawa & Frick, 2006a), missing items were imputed only if at least one item was present.’

2.3 The Adolescent Brain and Cognitive Development Study (ABCD)

2.3.1 Overview and Aims

The data presented in Chapter 5 have been collected as part of The Adolescent Brain and Cognitive Development Study (ABCD), a collaborative effort across various national institutes of health (NIH), uniting diverse research agendas and expertise to address urgent public health inquiries (Volkow et al., 2018). The ABCD consortium aimed to explore: i) how substance use and other experiences during childhood and adolescence influence brain development, ii) how these experiences promote or confer risk to long-term health outcomes, and iii) the complex interactions between environmental exposures and development (Volkow et al., 2018). This collaboration comprises a Coordinating Centre, a Data Analysis, Informatics & Resource Centre, and 21 research sites situated throughout the US (Figure 2). These research sites have extended invitations to 11,880 children aged 9-10 to participate in the study. These participants will be followed for 10 years, with annual lab-based and biennial MRI assessments. Recruitment for the first wave started in 2016 and ended in 2018. Since then, releases of curated, anonymized data and associated computational workflows, are made available to researchers annually. As a result, ABCD's insights benefits not only mental health and substance use researchers but also educators, parents, physicians, and policymakers—effectively encompassing all those invested in the well-being of the youth. Below I will provide an overview of the recruitment protocols, as well as a description of key measures used in this chapter.

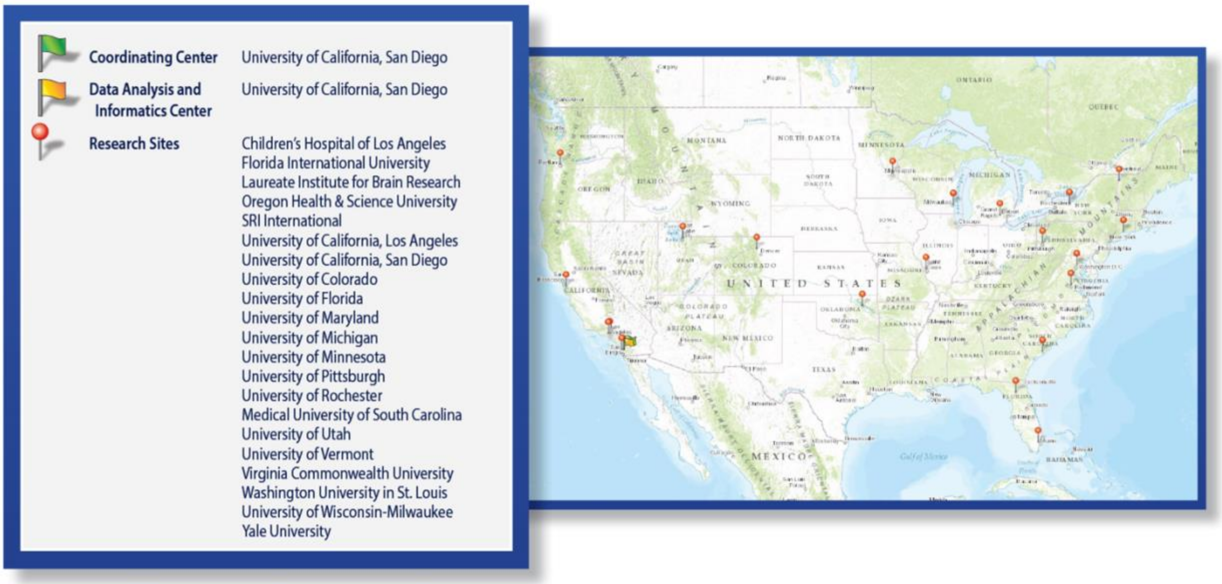


Figure 2. Locations of ABCD research sites in the United States

2.3.2 Recruitment

The ABCD study primarily recruited participants from elementary schools, encompassing both public (including charter) and private institutions. The recruitment targeted nine and ten-year-old children and their families, with the baseline assessments taking place between September 1st, 2016 and August 31st, 2018 (Garavan et al., 2018). This strategy aimed to engage a substantial portion of the young population and their families through the school system. Utilizing school demographic data, a standardized sampling approach was employed across all 21 participating sites. This school-based recruitment offered the advantage of facilitating direct interactions between researchers, children, and families. Methods such as classroom presentations, PTA meetings, and parent nights foster engagement, while teacher involvement contributes to long-term participant retention (Garavan et al., 2018).

2.3.3 Sampling procedures

Recruitment was initiated by establishing the catchment area for each research site's desired recruitment scope. Generally, these areas were defined geographically based on the proximity to the research facility (for example, all schools within a 50-mile radius of the research institution). An examination of the demographic composition of nine- and ten-year-olds residing in those catchment areas was conducted, along with an analysis of the demographic makeup of students in each elementary school (e.g., ethnic, gender compositions, and percentage of students receiving free or subsidized lunched as a proxy of SES) (Garavan et al., 2018). This was because it was important that the combined recruitment efforts generated a baseline cohort that closely mirrored the distributions of demographic and socio-economic attributes within the US. As the ABCD sample continued to grow, its demographic composition was closely monitored. Any emerging deviations from the intended targets were promptly recognized, and successful strategies from one site were disseminated throughout the consortium (usually intervening when deviations surpassed 10%). After schools have been identified, the research sites got in touch with school district superintendents and school principals to seek their collaboration in disseminating materials (both physical and electronic copies) to the nine- and ten-year-olds enrolled in their respective schools. Then, presentations led by researchers on adolescent development were provided to teachers, students, and parents. Furthermore, supplementary methods such as distributing study brochures and setting up information desks at school entrances were also employed to communicate the study's objectives effectively. Finally, to minimise the influence of systematic sampling biases, additional recruitment procedures (the source of <10% of the final sample) have also been employed. These included mailing lists, affiliates, referrals, and summer recruitment (e.g., outreach to summer activities and meal programmes) (Figure 3).

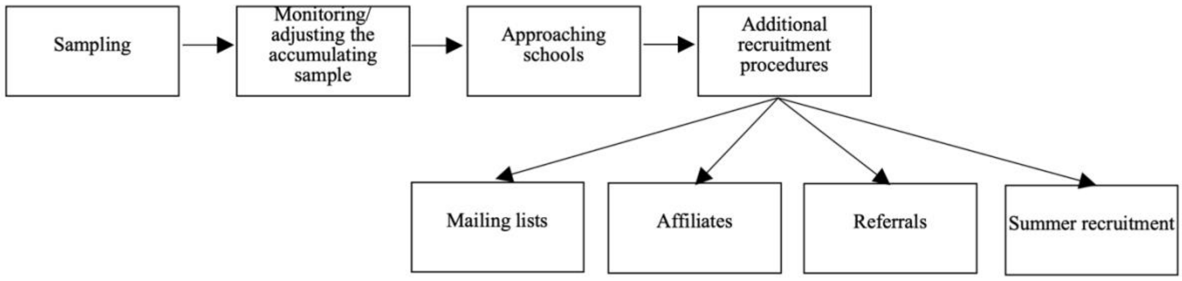


Figure 3. An overview of recruitment stages in the ABCD study

2.3.4 Consent

In the ABCD study, comprehensive consent procedures were implemented to ensure the ethical participation of all involved individuals. Parents or guardians provided written informed consent on behalf of minors aged 9 or 10, while minors themselves offered written assent. Participants above the specified age provided their own written informed consent. The consent process involves detailed explanations of the study's objectives, procedures, potential risks, and benefits. All data collection occurred within six months of obtaining informed consent, and the procedures aimed to uphold the well-being and privacy of participants throughout the study.

2.3.5 Key measures

2.3.5.1 Maltreatment

Unlike in Chapter 3 and 4, where childhood maltreatment was assessed using a single measure (i.e., the CBE), in Chapter 5, different measures for each subtype of abuse and neglect were used. This approach was in line with previous literature investigating adversity in the ABCD study (Stinson et al., 2021). The computerized Kiddie Structured Assessment of Affective Disorders and Schizophrenia (K-SADS) was used to evaluate exposure to physical, sexual, and emotional abuse for DSM-5 Post-traumatic stress disorder (PTSD) diagnosis (Kaufman et al., 1997a). The Parental Monitoring Questionnaire (PMQ; Chilcoat & Anthony,

1996) was employed to gauge physical and emotional neglect by assessing parental awareness of children's whereabouts and engagement in daily activities. Additionally, the Child Report of Parent Behavior Inventory (CRPBI; Schaefer, 1965), a 16-item survey, measured children's perceptions of caregiver warmth and support. A detailed description of these measures and their coding is provided in the Methods section of Chapter 5.

2.3.5.2 Psychopathology and grouping

To assess psychopathology, the same measures used in Chapter 3 and 4 were also employed in Chapter 5 - The CBCL (Achenbach & Ruffle, 2000) and the K-SADS-PL (Kaufman et al., 1997a). Moreover, participants were divided into four mutually exclusive groups following the same procedure employed in Chapter 3 and 4.

2.3.6 Covariates

The analyses in Chapter 5 also accounted for IQ and SES, but these were measured differently from the FemNAT-CD study. A description of their operationalization, as well of other covariates specifically used in this analysis (i.e., intracranial volume) are described in Chapter 5.

2.3.7 Imaging Equipment

The ABCD imaging protocol has been standardized for three different 3T scanner platforms: Siemens Prisma, General Electric (GE) 750, and Philips. This standardization involved the use of multi-channel coils capable of performing multiband echo planar imaging (EPI) scans, utilizing a regular adult-size coil. The decision to opt for a standard head coil across all age groups on each scanner platform, instead of using specialized nonstandard coils, was based on several reasons. Firstly, the brains of 9- and 10-year-olds typically range from 90% to 95% of adult brain size. This empirical observation supported the practicality of utilizing a shared stereotactic space for this age group, consistent with that used for adults as well (Burgund et al., 2002; Kang et al., 2003). Secondly, implementing age-specific customized coils would have introduced considerable complexities in the analysis process, potentially leading to confusion where coil-related effects could be entangled with age effects. Lastly, the implementation of customized coils necessitated the manufacturer to create and provide these tailored coils and connectors. However, obtaining such customizations across all sites during the initial year of optimizing and harmonizing the scanning protocol proved unfeasible. From the inception of the ABCD study in September 2016, maintaining stability in the hardware has been of utmost importance. Close coordination with equipment vendors has been a priority to ensure hardware stability throughout the entirety of this 10-year study.

2.3.8 Image acquisition protocol

The ABCD image acquisition protocol involved obtaining structural (sMRI), diffusion (dMRI), and functional (fMRI) data (Figure 4).

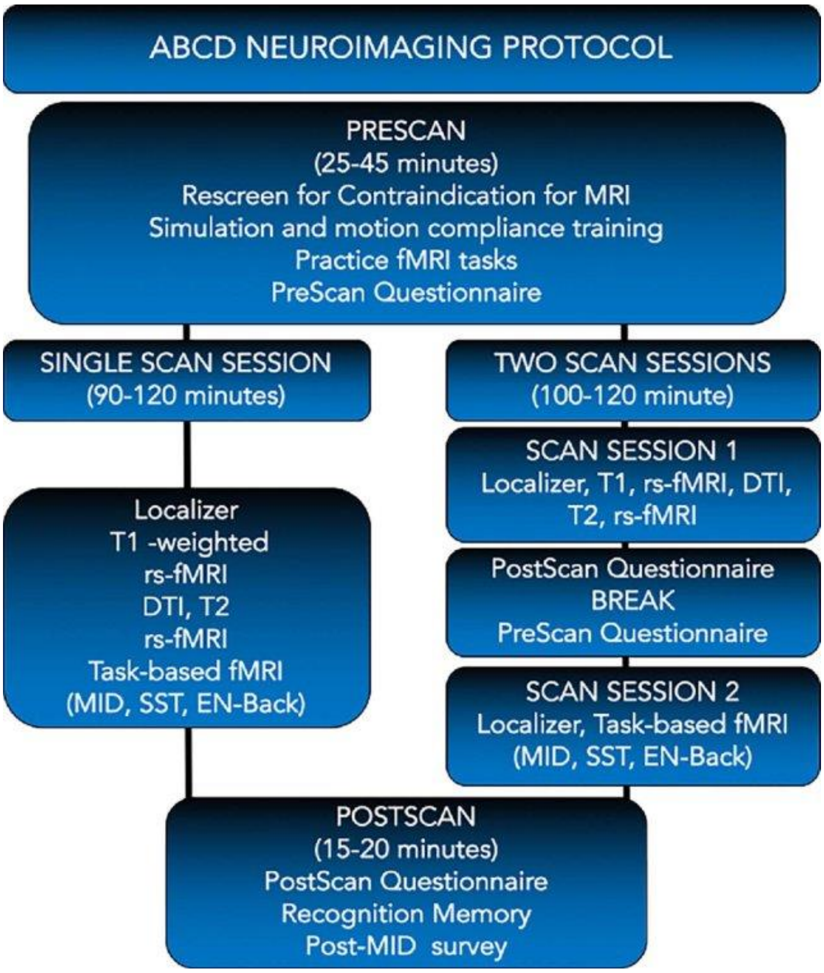


Figure 4. The ABCD Neuroimaging Protocol. From Casey et al., (2018), *Developmental Cognitive Neuroscience*, 32, 45. Reprinted with permission.

There were five general stages in the processing and analysis pipeline (Hagler et al., 2019)

i) Image files compliant with the Digital Imaging and Communications in Medicine (DICOM) standards were organized by series and categorized based on extracted metadata from the headers. They were then converted into compressed volume files containing one or more frames (time points). The protocol compliance was automatically checked, and confirmation of the expected file count per series was verified.

ii) Images underwent corrections for distortions and head motion. Cross-modality registrations were also performed for alignment.

iii) This stage involved reconstructing the cortical surface and segmenting subcortical and white matter brain regions.

iv) Modality-specific analyses were conducted at the individual subject level. Imaging-derived measures were extracted, employing various regions of interest (ROIs).

v) Analysis outcomes for ROIs were aggregated across subjects and presented in tabular format for summarization (Figure 5).

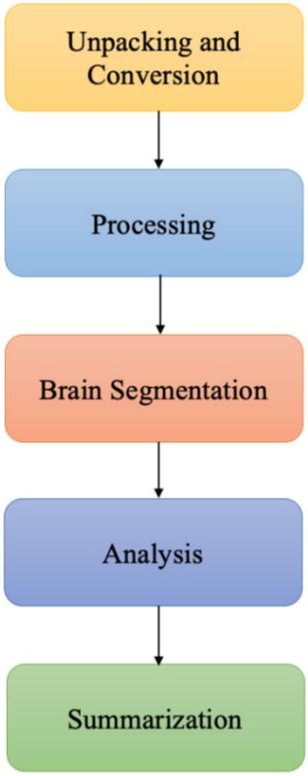


Figure 5. The five stages of MRI processing and analysis pipeline

2.3.9 sMRI preprocessing

T1-weighted (T1w) and T2-weighted (T2w) structural images underwent correction for gradient nonlinearity distortions using specialized nonlinear transformations provided by MRI scanner manufacturers (Jovicich et al., 2006; Wald et al., 2001). T2w images were aligned with T1w images through mutual information registration (Wells et al., 1996) following initial coarse, rigid-body alignment via within-modality registration to atlas brains. A common artifact in MR images is spatially varying intensity irregularities (receive coil bias), leading to inconsistent intensity patterns. Standard correction methods, such as those utilized by FreeSurfer (Dale et al., 1999; Fischl, 2012; Sled et al., 1998), were insufficient when correcting steep spatial intensity variations. This can cause inaccuracies in brain segmentation and cortical surface reconstruction. To address these issues, a novel implementation was employed for intensity inhomogeneity correction. Estimated B1-bias fields, computed using sparse spatial smoothing and white matter segmentation, were applied to normalize T1w and T2w intensities across participants. This ensured white matter voxel intensities centered around a target value of 110 after bias correction, while other voxel intensities were scaled accordingly. This target value aligns with FreeSurfer's bias correction standard. The white matter mask, established through an atlas-based segmentation method, was refined using a neighbourhood filter to exclude intensity outliers.

A linear inverse with regularization, facilitated by an efficient sparse solver, was utilized to estimate the smoothly varying bias field. This estimation took place within a smoothed brain mask that was interpolated linearly along the inferior-superior axis, avoiding abrupt intensity changes between brain and neck regions. Images were then rigidly registered and resampled to align with a standardized reference brain in standard space. This reference brain, previously created in-house, had 1.0 mm isotropic voxels, and was roughly aligned with the anterior commissure/posterior commissure (AC/PC) axis.

Quality control (QC) was performed before full image processing, and scans failing manual QC were excluded. If multiple scans of a certain type were available, the one with the fewest issues was chosen for processing. In case of a tie, the last acceptable scan of the session was used. Most participants in the ABCD study provided one scan per type (T1w or T2w), ensuring consistency, and minimizing processing variability. For a detailed description of the imaging procedure, protocol, and ordering of scans, please refer to (Casey, 2018).

Chapter 3

Note: This chapter has been published in the *European Child and Adolescent Psychiatry* (ECAP) journal: Diaconu, B., Kohls, G., Rogers, J. C., Pauli, R., Cornwell, H., Bernhard, A., ... & De Brito, S. A. (2023). Emotion processing in maltreated boys and girls: Evidence for latent vulnerability. *European Child & Adolescent Psychiatry*, 1-14.

CHAPTER 3 – EMOTION PROCESSING IN MALTREATED BOYS AND GIRLS: EVIDENCE FOR LATENT VULNERABILITY

3.1 Introduction

Childhood maltreatment refers to any act of omission (neglect) of care or commission (abuse) that results in actual or potential harm, regardless of intent (Gilbert et al., 2009). Maltreatment is associated with negative cognitive, psychological and medical outcomes and is a reliable and important predictor of poor mental and physical health (Korbin & Krugman, 2014). Maltreatment may alter certain developmental mechanisms such as those related to emotion processing, potentially leading to a cascade of negative consequences (Harms, Leitzke, & Pollak, 2019.). Indeed, these negative health outcomes have been hypothesized to be partly mediated by the numerous neurocognitive and neurobiological alterations associated with maltreatment that are thought to confer latent vulnerability (Catale et al., 2020; Hoeijmakers et al., 2018; McCrory et al., 2017). While in the short term, these alterations may have adaptive value, especially in adverse environments, in the long term they can become maladaptive, leading to various psychiatric disorders across the lifespan (McCrory et al., 2017). The aim of the current study was to test for differences in emotion processing in youth with a history of maltreatment. We focused on facial expression recognition and reward/punishment emotion learning. Critically, we controlled for the presence of psychopathological symptoms, to ensure our findings are a true reflection of latent vulnerability in maltreated youth. Finally, we also explored sex differences in the way latent vulnerability is manifested.

Emotion recognition is the ability to recognize displays of emotions based on non-verbal information, such as facial expressions. Emotion recognition is an essential part of social communication. For example, accurate recognition of expressions serves as an important cue for trustworthiness or intent (Hepp et al., 2021). Research suggests that maltreatment is associated with altered emotion processing, but findings have been inconsistent (B. L. Blair et al., 2015). A meta-analysis of studies assessing the ability to recognize facial expressions by children and adults with a history of maltreatment showed an overall impairment (Luke & Banerjee, 2013). Though it is worth noting that out of 24 studies identified, seven reported impaired emotion recognition following maltreatment, three reported a superior emotion recognition, while 14 were excluded for lacking information about effect sizes. A qualitative integration of all 24 studies showed a more complex pattern. For example, one study reported that maltreated youth showed increased recognition for anger (Shackman & Pollak, 2005), fear and sadness (Leist & Dadds, 2009), whereas others indicated reduced recognition for fear (Pajer et al., 2010). A more recent review (da Silva Ferreira et al., 2014) on facial emotion recognition in maltreated children reported that five of the nine studies indicated a reduced global emotion recognition in maltreated youth, with only one study (Pollak et al., 2000) reporting a specific impairment for negative emotions. Finally, a recent meta-analysis (Saarinen et al., 2021) focusing on the recognition of sad, happy, fearful and angry expressions in individuals with adverse experiences (e.g., maltreatment, war, illness) before the age of 18 years showed that adverse events pre-adulthood were associated with impaired recognition for fear and happiness. Taken together, this literature suggests that maltreatment is associated with a reduced ability to recognize particular emotions, specifically fearful and happy expressions, but there is high heterogeneity across studies.

Emotion learning refers to the ability to adjust responses following feedback, which can be rewarding (positive) or 'punishing' (negative) and participants learn the reinforcement contingencies to maximize rewards and minimize punishment (Schoenbaum & Roesch, 2005). It is suggested that childhood maltreatment alters the learning environment through exposure to extreme parental affective reactions and inconsistency of reinforcers (Hanson et al., 2017). This can lead to unpredictable or extreme contingency learning and biased attention towards negative cues. A systematic review of the impact of early/ childhood adverse effects on emotion learning in animals report that following maternal separation, rats and monkeys show weaker reward-based learning. Similarly, most of the research in humans to date has focused on the association between general adverse childhood experiences and stimulus-reinforcement learning, particularly reward based learning (Novick et al., 2018). For example, a study investigating eye movements in monetary incentive (reward-winning and punishing-losing) and non-incentive conditions showed that youth exposed to early-life stress (e.g., adoption, emotional neglect), exhibited slower responses than controls and failed to show reward incentive-related improvement on trials requiring inhibitory-saccade control (Mueller et al., 2012). Similarly, relative to typically developing youth, those with a history of adverse life events earned less points on reward incentive trials; this was specifically observed for food insecurity but not neglect (Dennison et al., 2019a; Kasparek et al., 2020). Another study showed that adolescents exposed to early life stress are slower to learn positive and negative stimulus–response associations (Harms et al., 2018). One longitudinal study showed that maltreatment and cumulative early adversity were associated with impaired punishment-based emotion learning and antisocial behaviour (Yazgan et al., 2021). However, this study did not examine responses to rewarding stimuli. Consistent with the above behavioural data, recent fMRI work has shown that early life stress exposure is associated with reduced rewards responsiveness in brain regions such as striatum, orbitofrontal, and medial frontal cortices, and increased response to punishment within the striatum, somatosensory and the lateral frontal cortices (Birn et al., 2017; K. S. Blair et al., 2022; Gerin et al., 2017). Taken together, the above studies suggest that maltreatment reduces reward-based learning, but possibly increases punishment-based learning. However, this is mostly based on the results of studies that have examined response to either reward or punishment separately, but not both components in the same task.

An important limitation for our understanding of how maltreatment impacts emotion processing is the high comorbidity of maltreatment with psychopathology. Indeed, maltreatment is associated with internalizing and externalizing psychopathology, which have themselves been linked to emotion recognition (Kohls, Baumann, et al., 2020; Leist & Dadds, 2009) and learning deficits (Guyer et al., 2006; Kohls, Baumann, et al., 2020). Only a few behavioural studies have examined both maltreatment and psychopathology and how they relate to emotion recognition (Saarinen et al., 2021) and learning (Mueller et al., 2012; Novick et al., 2018) in the same individual. The meta-analysis (Saarinen et al., 2021) examining the impact of early adverse effects on expression recognition, outlines that the results from studies who report psychiatric diagnosis of the maltreated participants did not differ from those who did not. Similarly, for emotion learning, the presence of psychopathology symptoms did not affect the responses of youth with adverse history to incentive trials (Dennison et al., 2019a; Kasparek et al., 2020; Mueller et al., 2012). However, in most of the above studies maltreatment and psychopathology were often completely overlapping, making it impossible to disentangle the source of the deficits. One way to clarify the respective effects of maltreatment from psychopathology is to separate youth who have been exposed to maltreatment into those with and without psychopathology symptoms. This would enable to answer the question, of whether in the absence of overt psychopathological symptoms childhood maltreatment scar individuals, making them more vulnerable. According to the theory of latent vulnerability (Catale et al., 2020; Hoeijmakers et al., 2018; McCrory et al., 2017), maltreatment is associated with alterations in various neurobiological systems, which are thought to support short-term functional adaptation in the context of maladaptive environments. However, in the long term these alterations are associated with poor optimization to more adaptive environments, conferring risk to poor mental health. This means that it is possible for an individual to show resilience (no psychopathological symptoms) at one point in time, but still exhibit system alterations (i.e., latent vulnerabilities) that could, at a later point in time become detrimental for social functioning. As such, clarifying whether these alterations exist in maltreated youth who are resilient would enhance our understanding of the specific candidate neurocognitive systems that may increase vulnerability following maltreatment (McCrory et al., 2017) .

Beyond psychopathology, maltreatment can also have differential sex effects on emotion processing. There is a large body of evidence suggesting the two sexes differ in the way they respond to stress (Bangasser & Wiersielis, 2018; Kudielka & Kirschbaum, 2005). Furthermore, studies from healthy individuals show that females are better at emotion recognition than males (Thompson & Voyer, 2014), and males outperform females in emotion learning (Evans & Hampson, 2015). However, the potential influence of sex on the association between maltreatment and emotion recognition/learning is understudied because of small samples providing insufficient statistical power. This is a major limitation given that sex has been shown to impact both the nature and severity of psychiatric outcome following maltreatment. Specifically, maltreatment-related psychiatric disorders are associated with a greater prevalence of internalizing psychopathology in females, and greater prevalence of externalizing psychopathology in males (Rutter et al., 2003). While some evidence suggest that maltreatment has a more detrimental effects on males (Keyes et al., 2012; McClure, 2000), other suggest a stronger effect on females (Thomas et al., 2022). The current study aims to revisit the impact of maltreatment on emotion processing by explicitly considering the influence of psychopathology and sex. We divided participants into four groups based on presence/absence of maltreatment history and psychopathology symptoms and used the emotion hexagon task (Calder et al., 1996) for assessing facial emotion recognition, and the passive avoidance learning task (Newman & Kosson, 1986) as an index of emotion learning.

Given the available literature, we formulated the following hypotheses:

i. For emotion recognition, we expected to replicate the findings from the latest meta-analysis and find maltreatment to be associated with reduced recognition for both negative (fear) and positive (happiness) emotions (Saarinen et al., 2021).

ii. For emotion learning, we expected to observe disrupted reward-based learning in maltreated youth (i.e., more omission errors) and increased punishment learning (i.e., less commission errors).

iii. For both tasks, based on the latent vulnerability hypothesis, we expected to observe differences between the resilient (i.e., maltreated, low psychopathology) and the control group.

iv. Given evidence that psychopathological profiles associated with maltreatment differ between the sexes, we hypothesized that this would manifest as different profiles of emotion processing. However, we did not formulate a specific hypothesis regarding the direction and nature of the differences.

3.2 Methods

3.2.1 Participants

The FemNAT-CD study (Freitag et al., 2018) (N = 1827) included 11 sites across Europe. Participants were recruited via community outreach, mental health clinics and youth offending services, with an effort to optimize recruitment of females. Participants were recruited if they were within the age of 9–18 years. Participants with an IQ < 70 or with a diagnosis of autism spectrum disorder, schizophrenia, neurological conditions, and genetic syndromes were excluded. Typically developing participants were excluded if they had any psychiatric diagnosis. For the current study, 828 youth (514 females) aged 9–18 years (M = 13.8; SD = 2.5) completed the emotion hexagon task (Calder et al., 1996). (See Appendix 1 for the distribution by group, sex and site and Appendix 2 for inclusion criteria). Of these, 717 youth (446 females) also completed the emotion learning task (Newman & Kosson, 1986). (See Appendix 3). Written informed consent/assent was obtained from all participants and their parents according to site-specific ethical requirements.

3.2.2 Measures

Consistent with previous maltreatment research (Lansford et al., 2002), youth were divided into maltreated and non-maltreated groups using the Children's Bad Experiences Questionnaire (CBE). The CBE is a 5-item semi-structured interview in which the informant (parent, caregiver, or guardian) is asked to provide information about the child's experiences of physical, psychological, and sexual harm. The interviewers did not ask questions about the perpetrator of abuse, with a focus on whether these forms of maltreatment had been experienced by the child or not. The informant had the option to answer these questions with "Never", "Yes", "Frequent" or "I don't know/Refuse to Answer", followed by a detailed description of the event whenever applicable. Finally, based on all the information collected, a decision was made as to whether no/probable or definite maltreatment had been reported. In line with previous research using this instrument, participants were classified as 'maltreated' if probable or definite maltreatment was reported.

Psychopathology was assessed via the Child Behaviour Checklist (CBCL) (Achenbach & Ruffle, 2000) and the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997a). The CBCL is a checklist completed by parents/caregivers to examine eight dimensions: anxiety/depression, withdrawal, somatic complaints, thought problems, attention problems, rule-breaking behaviour, and aggressive behaviour. Overall scores were used for analysis, with T scores > 65 as the clinical cut-off point (Mazefsky et al., 2011). The K-SADS-PL is a semi-structured diagnostic interview used to assess current and past psychopathology in children and adolescents (See Appendix 4 for inter-rater reliability information). Based on the above we classified participants to four groups: (1) control group: low psychopathology no maltreatment;

(2) maltreatment with low psychopathological symptoms (resilient group); (3) high psychopathology with no history of maltreatment: and (4) high psychopathology with a history of maltreatment (See Table 1, for demographic details and characteristics of each group).

Lastly, similar to our previous work (Rogers et al., 2019), puberty status was assessed using the Pubertal Development Scale (PDS) (Robertson et al., 1992), and IQ was estimated using the Wechsler Intelligence Scales (WASI, WAIS, WISC) (Climie & Rostad, 2011). In English-speaking sites, IQ was estimated with the vocabulary and matrix reasoning subscales of the WASI-I. Other sites used the vocabulary, block design and matrix reasoning tests of the WISC (for participants aged ≤ 16) or WAIS (for participants aged 17–18 years).

Table 1. Participants' Demographic Characteristics and Psychopathology Subscales Scores

	Control	Resilient	High Psychopathology	Psychopathology + Maltreatment	Group effects
Sample	**N=516**	**N=30**	**N= 172**	**N=110**	**F/x²**
Age, M (SD)	13.7 (2.6)	13.9 (2.7)	13.9 (2.4)	13.8 (2.3)	0.4
Females (in %)	62.8	70.2	57.8	59.7	2.7
Estimated Full-scale IQ, M (SD)	105.4 (11.7) [a]	104.3 (13.9) [a]	97.9 (11.6) [b]	98.4 (13.7) [b]	26.6***
Estimated Verbal IQ, M (SD)	105.3 (14.9) [a]	103.2 (18.9) [a]	96.6 (13.6) [b]	95 (17.4) [b]	26.6***
Estimated Performance IQ, M (SD)	104.8 (13.7) [a]	104.8 (13.5) [a]	98.7 (14.4) [b]	101.3 (14.8) [a]	10.9***
PDS (1=pre/early puberty; 2=mid/late/post puberty) (in %)	2 – 81.3	2 – 75.6	2 – 80.2	2 – 82.2	0.6
SES M (SD)	0.3 (0.9) [a]	0.2 (1.1) [a]	-0.2 (1.1) [b]	-0.4 (1.1) [b]	29.5***
CBCL Total t scores M (SD)	48.1 (8.5) [a]	52.4 (7.8) [a]	73.9 (6.5) [b]	75.1 (6.1) [b]	838.8***
CBCL Internalizing Scale	47.7 (8.3) [a]	53.8 (8.7) [a]	70.3 (11.9) [b]	74.4 (7.9) [c]	480.2***
CBCL Externalizing Scale	49.8 (8.5) [a]	53.5 (8.4) [a]	68.2 (8.6) [b]	70.3 (8.4) [b]	367.8***
CBCL Anxiety/Depression	53.3 (5.1) [a]	55.4 (6.4) [a]	65.5 (10.7) [b]	69.6 (9.6) [b]	242.3***
CBCL Withdrawal	53.6 (5.3) [a]	55.1 (5.5) [a]	65.1 (10.2) [b]	67.7 (9.0) [b]	206.3***
CBCL Somatic Complaints	54.6 (5.8) [a]	57.1 (6.9) [a]	64.3 (10.1) [b]	64.9 (11.1) [b]	110.2***
CBCL Social Problems	52.7 (4.7) [a]	54.9 (6.6) [a]	65.8 (10.2) [b]	68.8 (9.8) [b]	273.1***
CBCL Thought Problems	52.3 (4.6) [a]	53.4 (5.8) [a]	66.4 (10.4) [b]	66.2 (10.3) [b]	263.9***
CBCL Attention Problems	52.9 (5.1) [a]	54.3 (4.9) [a]	68.5 (10.2) [b]	71.9 (10.1) [b]	375.8***
CBCL Rule-breaking Behavior	52.5 (4.5) [a]	54.8 (5.4) [a]	70.2 (11) [b]	74.4 (11.9) [b]	496.1***
CBCL Aggressive Behavior	52.6 (4.5) [a]	56.2 (6.6) [a]	72.2 (11.8) [b]	75.5 (10.6) [b]	496.1***

Notes: Control = No Maltreatment, Low Psychopathology; Resilient= Probable/Definite Maltreatment, Low Psychopathology; High Psychopathology=No Maltreatment, High Psychopathology; Psychopathology + Maltreatment = High Psychopathology, Probable/Definite Maltreatment; SES = Socioeconomic Status (SES was computed based on parental income, education level and occupation); CD = Conduct Disorder (Diagnosis of CD was based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Lifetime and Current versions (KSADS-L/C); PDS = Pubertal Developmental Status; CBCL = Child Behavior Checklist; The CBCL scores for the Internalizing scale were computed using the Anxiety/Depression, Withdrawal and Somatic Complaints subscales, whereas the scores for the Externalizing scale were computed using the Rule-breaking and Aggressive Behavior subscales; SEM = Standard Error of the Mean; Post-hoc tests are reported based on observed means, where groups marked with different letters differ significantly from each other at **p*<.05, ***p*<.01 and ****p*<.001.

3.2.3 Experimental paradigms and dependent variables

Emotion recognition accuracy (in percent) of facial expressions was assessed using the Emotion Hexagon task, (Calder et al., 1996) including happy, sad, angry, fearful, disgusted, and surprised expressions. The dependent variable for this task was accuracy of emotion recognition (in %), for the dominantly presented emotion (e.g., 70% or 90% anger). For emotion learning, we used a modified Passive Avoidance Learning task (Newman & Kosson, 1986) where participants had to learn by trial-and-error to respond to stimuli eliciting rewards (winning points) and to avoid responding to stimuli eliciting punishments (losing points). Incorrect responses to punishment stimuli were counted as commission errors and missed responses to reward stimuli were counted as omission errors. More details on the test battery can be found in Figure 6. (See Appendix 5 for details on task randomization).

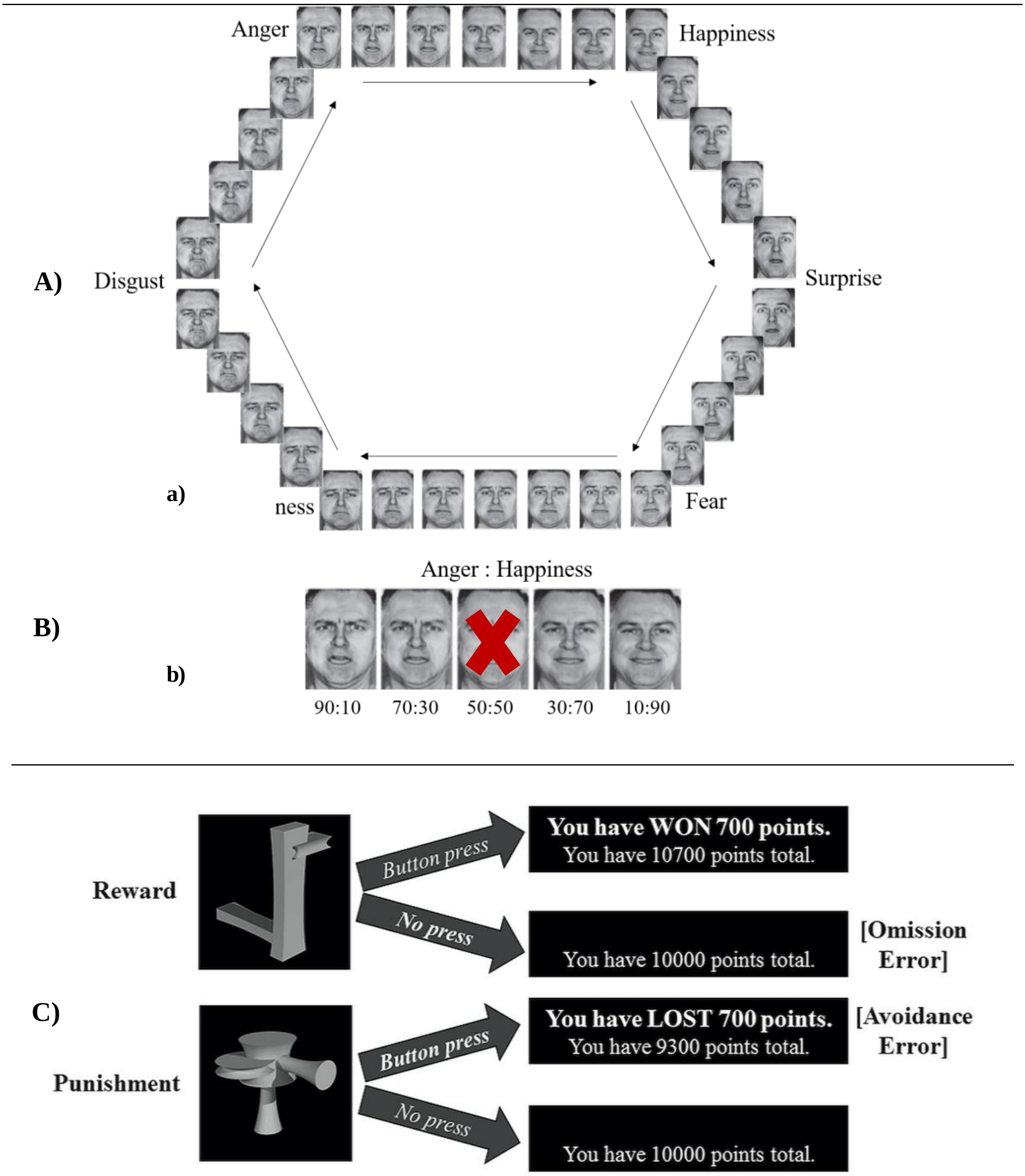


Figure 6. Schematic representations of the Emotion Hexagon and the Passive Avoidance Learning Tasks.

Notes: A) The complete set of blended expressions arranged in a hexagon. The six basic emotions (anger, happiness, surprise, fear, sadness, and disgust) lie on the vertices adjacent to their most easily confused emotion. The faces on the edges of the hexagon are the blended expressions used as task stimuli. **B)** An example of the blended expressions for the anger-to-happiness continuum, with anger: happiness ratios labelled. Each continuum was presented with percentages of expressed emotions varying from 10 to 90% (e.g., 10% surprise–90% happiness, 30% surprise–70% happiness). Stimuli were presented using E-Prime on a computer monitor in random order for three seconds and participants were asked to select the label that best described the emotion presented. The ‘dominant’ emotion (i.e., 90% or 70% present) was considered the correct response. Response time was not constrained, and no feedback was provided. The task included six blocks, each containing two 90% and two 70% expression morphs for each emotion, resulting in four correct instances of each expression per block. The first block was for practice, leaving only five blocks for analysis. Participants took approximately 20 minutes to complete this task. The 50-50% morphs were fillers and not scored. **C)** A schematic representation of the Passive Avoidance Learning Task using novel ‘ziggerin’ stimuli. Four stimuli were associated with reward and four with punishment fixed values (1, 700, 1400, 2000 points). Each stimulus was shown once within a block of 8 trials, with 10 blocks overall (including one practice block, excluded from analysis). Stimuli were displayed on a computer monitor for a maximum of 3 seconds, followed by performance feedback (i.e., points won or lost or no change, as well as the running total). Participants started the task with 10,000 points. The average completion time for this task was 5 minutes.

3.2.4 Statistical analyses

For the Emotion Hexagon task, we used a 2 (Maltreatment: no vs. probable/definite) by 2 (Psychopathology: low vs. high) by 2 (Sex: male vs. female) by 6 (Emotions: anger, happiness, surprise, fear, sadness, and disgust) design. For the Passive Avoidance task, the design was a 2 (Maltreatment: no vs. probable/definite) by 2 (Psychopathology: low vs. high) by 2 (Sex: male vs. female) by 4 (Magnitude: 1, 700, 1400 or 2000 points) for both omission and commission errors. Repeated measures analyses of covariance (rmANCOVA) were used to analyse the accuracy data, with mean centred IQ, SES, and pubertal status (pre/early puberty vs. mid/late/post puberty) as covariates of no interest. To account for differences between sites of data collection, we re-run the analyses by including the sites with the largest number of participants (i.e., Germany and United Kingdom, N = 576; Appendix 6). Significant main effects of interactions were followed by pair-wise post hoc comparisons using Bonferroni correction. Effect sizes are reported as partial eta squared (ηp2), interpreted as follows: small ≥ 0.01; medium ≥ 0.06; large ≥ 0.14 (J. Cohen, 1988).

3.3 Results

3.3.1 Emotion recognition

For simplification, we only report significant main effects and interactions involving maltreatment, psychopathology, and sex, as per our aims. (See Appendices 7 and 8 for pubertal status and age results). For accuracy, the rmANCOVA revealed significant main effects of psychopathology, maltreatment, and sex (Table 2). Both maltreatment and psychopathology were associated with significantly decreased accuracy and females were significantly more accurate than males. There were also significant two-way interactions between emotion and maltreatment, and a three-way interaction between emotion, maltreatment, and psychopathology. For the two-way interaction, post-hoc analyses indicated that maltreated youth were significantly less accurate than non-maltreated youth when recognizing fear, but no significant differences were found for the other emotions (Figure 7a). However, for the three-way interaction, post hoc analyses showed that when psychopathology levels were low, maltreated youth were significantly less accurate than non-maltreated youth when recognizing happiness, fear, and disgust. When psychopathology levels were high, no significant differences were found between maltreated and non-maltreated youth for any emotion (Figure 7b, c). Lastly, we also found a three-way interaction between sex, emotion, and maltreatment. Post-hoc analyses indicated that maltreated females were less accurate for happiness and fear compared to non-maltreated females. Maltreated males were less accurate for fear, and disgust compared to non-maltreated males. (Figure 8) (See Appendix 9 for additional analyses on females only).

Table 2. Main and interactive effects of maltreatment, psychopathology and sex on emotion recognition and learning

		Emotion Recognition			
Main effects	***F***	***df***	***p***	η_p^2	***Post-hoc comparisons***
Maltreatment	3.94	1, 808	.047	.005	-
Psychopathology	5.45	1, 808	.020	.007	-
Sex	20.93	1, 808	*p*<.001	.025	-
2-Way Interactions					
Emotion by Maltreatment	2.41	5, 4040	.034	.003	**Fear**: Maltreated < Non-Maltreated Anger, Happiness, Surprise, Sadness, Disgust: n.s.
3-Way Interactions					
Emotion by Maltreatment by Psychopathology	2.25	5, 4040	.047	.003	Low Psychopathology: **Happiness, Fear, Disgust**: Maltreated < Non-Maltreated Anger, Surprise, Sadness: n.s. High Psychopathology: n.s.
Emotion by Sex by Maltreatment	2.98	5, 4040	.011	.004	**Females:** **Fear, Happiness:** Maltreated Females < Non-Maltreated Females **Males:** **Fear, Disgust** Maltreated Males < Non-Maltreated Males

(continued)

Table 2 Continued

			Emotion Learning		
Main effects	***F***	***df***	***p***	η_p^2	***Post-hoc comparisons***
Psychopathology	8.98	1, 707	.003	.013	-
Sex	4.83	1, 707	.028	.007	-
2-Way Interactions					
Sex by Maltreatment	4.68	1, 707	.031	.007	Maltreated Females > Non-Maltreated Females Maltreated Males < Non-Maltreated Males
Sex by Psychopathology	5.23	1, 707	.022	.007	High Psychopathology Males> Low Psychopathology Males Females: n.s.

Notes: For Emotion Learning, the rmANCOVA also yielded significant two-way interactions between sex and block and three-way interactions between sex, block and maltreatment, and sex, block and psychopathology respectively. For simplicity, we have not reported these results here, but they can be found in Appendix A10. However, the overall pattern of results showed that maltreated females made more avoidance errors than maltreated males during blocks 3,6,7, and 8, but by the 10th block, no significant sex differences were observed anymore. Interestingly, pairwise comparisons in the sex by block by psychopathology interaction showed that low psychopathology females made more avoidance errors during blocks 3,6,7, 8 than low psychopathology males, but no significant sex differences were found in any blocks when psychopathology was high. These analyses echo the rest of our reported results whereby maltreated females showed the most impaired performance on the emotion learning task. Covariates evaluated in the model were mean-centered SES = 0.125, IQ=1.245, and pubertal status (1 = pre/early puberty; 2 = mid/late/post puberty). The adjustment for multiple comparisons were obtained using the Bonferroni correction.

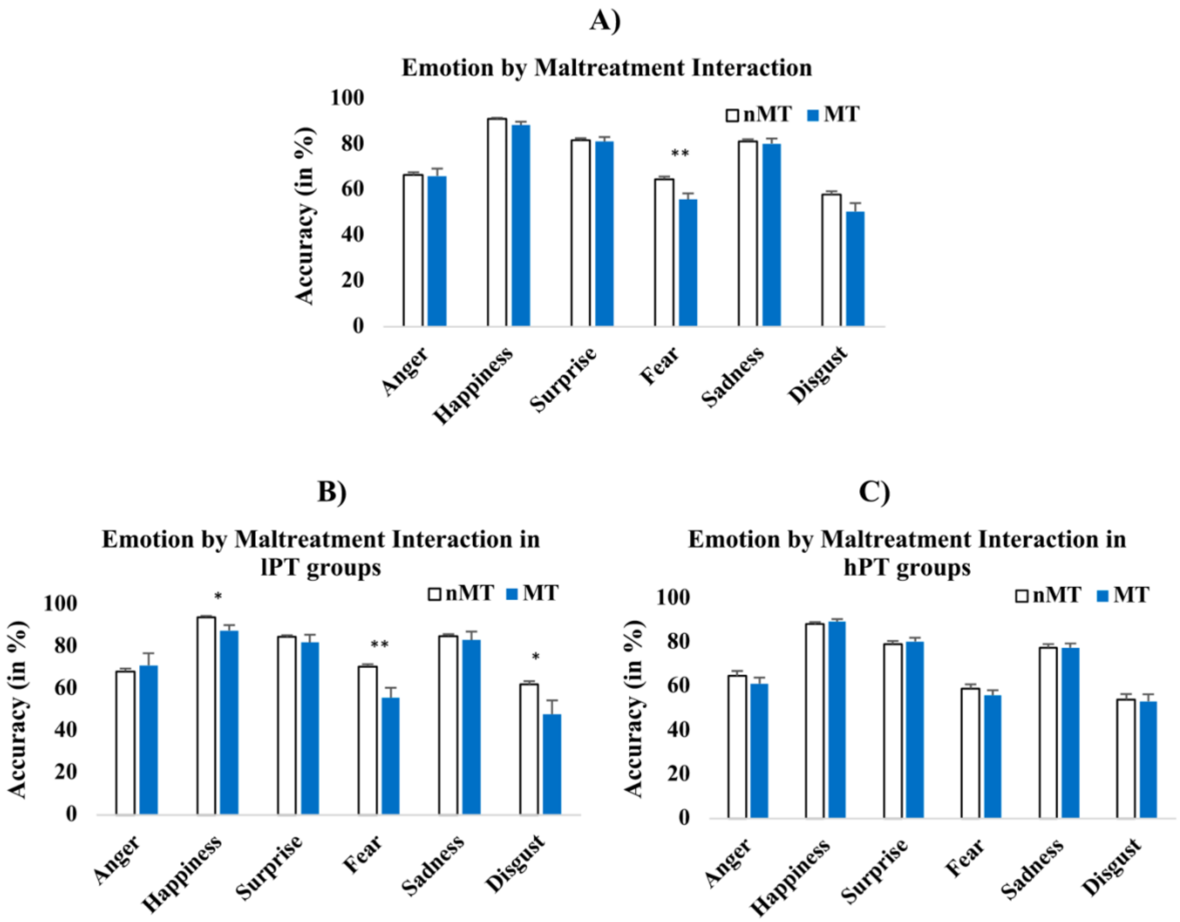


Figure 7. Interactive effects between maltreatment and psychopathology on emotion recognition.

Notes: A) Interaction between emotion and maltreatment for recognition accuracy; Maltreated (MT) youths are significantly less accurate than non-maltreated (nMT) youths when recognising fear (collapsing across the high and low psychopathology groups); **B)** Percentage accuracy across emotions between the nMT and MT groups when psychopathology was low (lPT); MT youths were significantly less accurate than nMT for happiness, fear and disgust. **C)** Percentage accuracy across emotions between the nMT and MT groups when psychopathology was high (hPT); Here, no significant differences were found between the nMT and the MT groups regardless of emotion. Groups differ significantly at $p<.05$ level (*), $p<.01$ (**), and $p<.001$ level. All error bars show +/- 1 standard error of the mean.

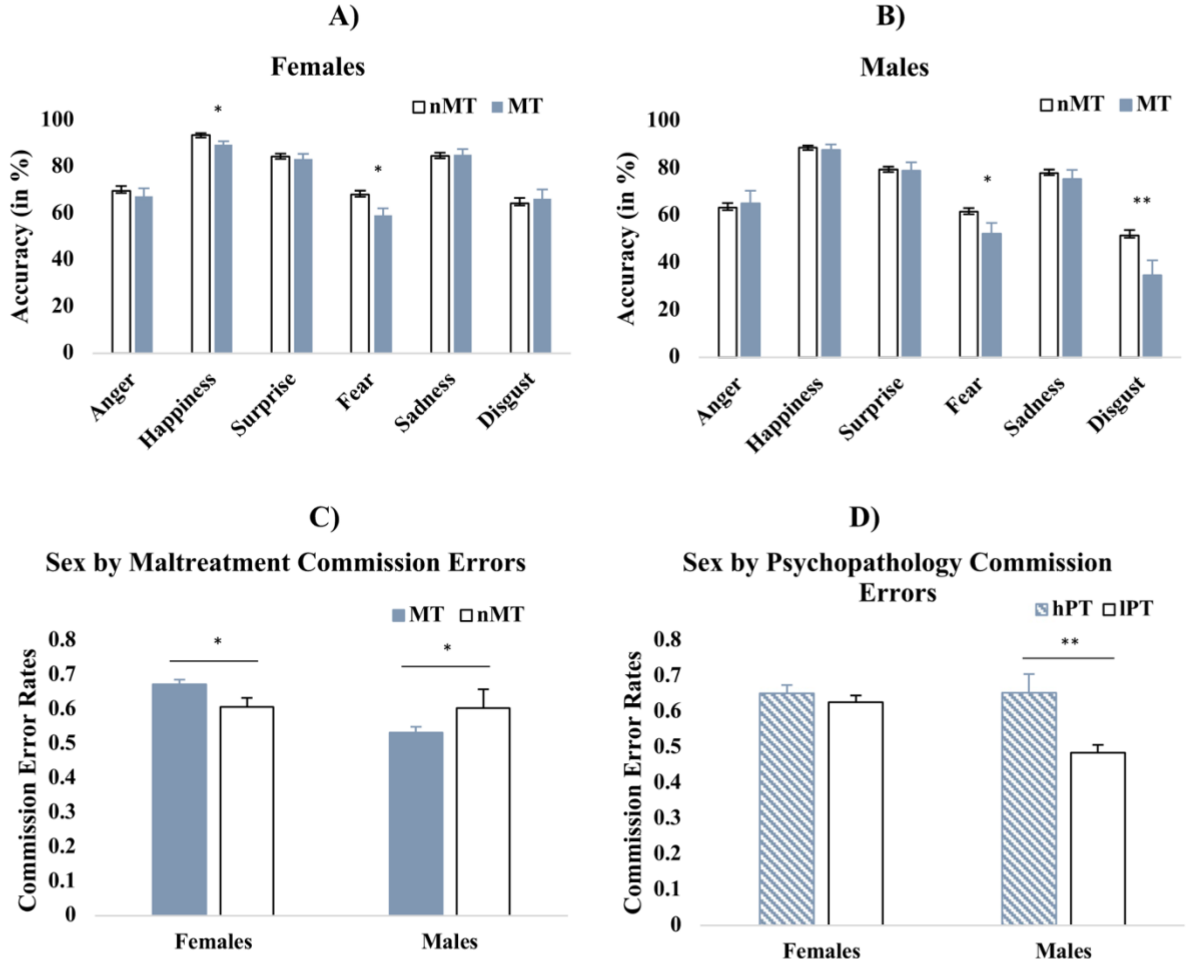


Figure 8. Interactive sex effects on emotion recognition and learning

Notes: A) Interaction between sex, maltreatment, and emotion on recognition accuracy; This panel shows the effects of MT in females. Here, MT females are significantly less accurate than nMT females for happiness and fear. **B)** This panel shows MT effects in males; here, MT males are significantly less accurate than nMT males for fear and disgust. **C)** Commission errors rates by sex and maltreatment. Here, maltreated females made significantly more commission errors than non-maltreated females, whereas maltreated males made less errors than non-maltreated males. **D)** Commission errors rates by sex and psychopathology. Females with low psychopathology did not significantly differ in their avoidance errors compared to females with high psychopathology, but high psychopathology males made more errors than low psychopathology males. Groups differ significantly at p<.001 (***), p<.01 (**), and p<.05 level (*). All error bars show +/- 1 standard error of the mean.

3.3.2 Emotion learning

For commission errors, the rmANCOVA revealed significant main effects of psychopathology, and sex (Table 2). Specifically, high-psychopathology youth made significantly more commission errors than low-psychopathology youth and females made significantly more errors than males. Significant two-way interactions were found between sex and maltreatment, and sex and psychopathology. Post-hoc analyses indicated that maltreated females made significantly more errors than non-maltreated females, whereas the opposite pattern was observed for males, where the non-maltreated males made more commission errors than the maltreated group. (Fig. 3c, d). Lastly, high and low psychopathology females did not significantly differ, but high psychopathology males made more errors than low psychopathology males (Table 2). For the results by block, please see Appendix 10. For omission errors, the rmANCOVA did not yield any significant main effects for either maltreatment or psychopathology. Similarly, no interactions were found between any of the other variables.

3.4 Discussion

Our study investigated emotion recognition and learning in maltreated and non-maltreated youth with and without psychopathology to address two aims. First, we wanted to clarify whether maltreated youth exhibit abnormities in emotion recognition and learning and to what extent the presence or absence of psychopathology would influence their neurocognitive profile. We hypothesized that maltreated youth would show reduced emotion recognition for fear and happiness. Our findings partially supported this, showing that maltreatment was specifically associated with a lower recognition of fear. Crucially, however, maltreatment, psychopathology and emotion interacted such that youth exposed to maltreatment and low levels of psychopathology showed deficits in happiness, fear and disgust recognition versus non-maltreated youth with low psychopathology. No differences between maltreated and non-maltreated youth were found when psychopathology was high. These findings support our third hypothesis suggesting a latent vulnerability effect for emotion recognition. For emotion learning, we hypothesized that maltreated youth would show reduced reward learning and increased punishment learning. This hypothesis was, however, not supported as indicated by the absence of significant main effects of maltreatment for reward-based learning and only a main effect of psychopathology for punishment-based learning; youth with high psychopathology made more commission errors than youth with low psychopathology. Second, we investigated whether sex interacted with maltreatment and/or psychopathology to predict emotion recognition and learning and hypothesized that maltreated males and females would exhibit different profiles of emotion processing. Consistent with that hypothesis, for emotion recognition we showed that maltreatment in females was associated with poorer recognition of happiness and fear, while in males, it was associated with a lower recognition of fear and disgust. For emotion learning, maltreatment was associated with more commission errors in females, but less commission errors in males.

The lower accuracy for both fear and happiness is consistent with the results of a recent meta-analysis of 29 studies (20 on youth aged 4.4–17.5) showing that maltreatment, particularly when experienced before the age of 3, was associated with reduced accuracy for those emotions, but not for sad or anger; unfortunately no data were available for disgust (Saarinen et al., 2021). However, our study is the first to show that maltreated youth who appear resilient on the surface might in fact exhibit a latent vulnerability in the form of lower emotion recognition for both negative (fear and disgust) and positive (happiness) basic emotions. Interestingly, and in contrast to our study, the above meta-analyses did not find a moderating effect of psychopathology (Saarinen et al., 2021). In terms of potential mechanisms, happy faces have been shown to facilitate social bonding and affiliation and are thus considered a form of social reward stimulus because they signal positive emotions, attachment availability, care, support, which all contribute to the development of trust (Nikitin & Freund, 2019; Todorov et al., 2009). Indeed, there is now good evidence indicating that trust is a prerequisite for successful social relationships and facial expressions are one of the main sources of information when forming an impression about someone’s trustworthiness (Balliet & Van Lange, 2013). Recent research suggests that relative to their peers, maltreated children are less likely to rate unfamiliar faces as trustworthy, which is thought to contribute to a reduced social network (Hepp et al., 2021; Neil et al., 2022). Thus, consistent with the latent vulnerability hypothesis, we speculate that the lower accuracy for happy faces in the resilient group indexes as a latent vulnerability, which long-term might reduce social affiliations via reduced trust, potentially increasing the risk for future psychopathology.

The resilient group also exhibited lower accuracy for fear and disgust faces, which, like happy faces, are reinforcers, but associated with potential threat and signalling that someone or something should be avoided (R. J. R. Blair, 2003). The reduced accuracy for those two negative facial expressions could thus reflect an avoidance bias. Indeed, previous studies investigating attention processes to threat in maltreated samples have identified an avoidance in processing fear, which may be caused by prolonged exposure to threatening or chaotic environments (Pine et al., 2005; Pollak & Sinha, 2002). This interpretation is supported by our additional analyses (see Appendix 11) on the confusability of emotion responses, which indicated that compared to controls, maltreated youth with low psychopathology (i.e., resilient) showed more bias towards disgust when fear was depicted. However, further research using eye-tracking would be needed to clarify whether our results do indeed reflect avoidance of these emotions.

In terms of emotion learning, contrary to our second and third hypotheses, we did not find a main effect of maltreatment on reward/punishment learning nor did we find that maltreatment and psychopathology interacted (i.e., no latent vulnerability). However, it is important to note that most behavioural studies reporting impaired reward learning investigated youth with experiences of early life stress (i.e., cumulative adverse experiences, not just sole maltreatment) (Hanson et al., 2017; Harms et al., 2018). Thus, our study adds to the literature by highlighting that maltreatment per se does not appear to be associated with impaired reward learning. Crucially, we also show for the first time that maltreatment and psychopathology do not interact to predict reward or punishment avoidance learning, which is suggestive of no latent vulnerability for that neurocognitive domain. Finally, psychopathology was associated with an impairment in punishment learning, which is in line with the current literature (Kohls, Baumann, et al., 2020). For instance, previous studies showed that subgroups with conduct problems exhibit reduced punishment learning compared to controls (Kohls, Baumann, et al., 2020). Some studies with adolescent samples indicate that this deficit may be specific to antisocial boys (Vitale et al., 2005), but previous work on the same dataset did not replicate these findings (Kohls, Baumann, et al., 2020).

In relation to our second aim, we found that sex interacted with maltreatment to predict performance in both emotion recognition and learning. Specifically, for emotion recognition, our study provides novel data indicating both similarities and differences in maltreated females and males. Indeed, we show for the first time that both maltreated sexes exhibit reduced recognition of fear, but that there are also sex differences such that females were impaired at recognizing happiness, while males were impaired at recognizing disgust. Since both maltreated males and females are at heightened risk of developing psychiatric disorders, similarities in their neurocognitive profile for fear recognition could reflect this. Interestingly, however, despite evidence that sex impacts both the nature and severity of psychiatric outcome following maltreatment, our supplementary analyses showed that our sample did not show sex differences in internalizing and externalizing psychopathology subtypes following maltreatment (Appendix 12).

The differences in recognizing happiness and disgust are also novel and suggest sex-dependent associations with maltreatment. Those findings are consistent with the literature suggesting that females and males respond to stress differently (Bangasser & Wiersielis, 2018; Kudielka & Kirschbaum, 2005) but here we show that sex differences in the neurocognitive profiles can be observed in maltreated youth specifically. Similarly, for emotion learning, our findings are novel and demonstrate a diametrically different profile across the sexes such that maltreated females made significantly more commission errors than non-maltreated females, whereas, surprisingly, maltreated males made less commission errors than non-maltreated males. Two previous studies using a similar task found lower punishment avoidance learning (i.e., lower correct rejection of punishment stimuli) in relation to maltreatment in boys (Mezzacappa et al., 2001) and to cumulative adverse experience in a mixed sex sample (Yazgan et al., 2021) while controlling for sex effects. Our findings clearly indicate that sex effects should be considered in future work investigating the association between maltreatment and emotion learning.

The strengths of our work can be divided into two categories. First, we included a large mixed-sex sample of youth who were comprehensively assessed using standardized measures for both maltreatment and psychopathology. Second, our unique design enabled us to clarify the main and interactive effects of maltreatment and psychopathology on emotion recognition and learning and test for sex effects. These findings, however, should be interpreted considering some limitations. First, by separating maltreatment from psychopathology, we inevitably obtained unequally sized groups. Specifically, the group with maltreatment and low psychopathology (i.e., resilient) was considerably smaller compared to the control and high psychopathology groups. Second, our effect sizes were rather small, which highlight substantial heterogeneity both within maltreatment and psychopathology. Third, the cross-sectional design precludes any causal inferences regarding temporal relation between maltreatment, psychopathology, and emotion recognition/learning and the extent to which emotion recognition performance in the resilient group reflects a true latent vulnerability for future psychopathology. Fourth, we assessed maltreatment based on interviews with parents/caregivers, who may not have been fully honest in reporting about maltreatment for social desirability reasons or may have been unaware that their child was abused. Fifth, our maltreatment measure (i.e., the CBE) does not distinguish between different subtypes of abuse (e.g., physical, or sexual), or the specific aspects of onset, severity, or chronicity of maltreatment. As such, we were not able to investigate their respective influences on emotion recognition and learning. However, these subtypes are often characterized by high co-occurrence, making it difficult to study them separately (Hanlon et al., 2020). Relatedly, while we did not distinguish between different forms of psychopathology (e.g., internalizing vs. externalizing) in our main analyses, we acknowledge that these may be associated with different emotion recognition profiles (Dennison et al., 2019a; McClure et al., 2003). Following a reviewer's suggestion, these post hoc analyses can be found in Appendix 12. Crucially, however, neither internalizing nor externalizing symptoms scores interacted with any other variables to predict emotion recognition nor emotion learning. Furthermore, our study design treating psychopathology as one category fits with the literature showing that mental disorders are better characterized by a general psychopathology dimension (i.e., p factor) (Caspi et al., 2014). Finally, it is important to mention that the FemNAT-CD study was aimed primarily at investigating sex differences in CD, meaning that all the youth in the psychopathology groups had CD. However, many of these youth were characterized by other forms of comorbidity, such as PTSD (much higher prevalence in the maltreatment group with high psychopathology than in the group with high psychopathology, but no maltreatment), ADHD or MDD (See Appendix 13). Moreover, recent research investigating CD (Kohls, Fairchild, et al., 2020) in the same dataset showed that only 23% of youth with CD show impairments in emotion recognition.

While considerable evidence points to the detrimental effects of maltreatment on children's emotional development, the inconsistencies in findings regarding emotion recognition and learning make it difficult to draw conclusions about their associations with maltreatment. Our study focused on disentangling the potential confounding effects of psychopathology from the effects of maltreatment on two domains of emotion processing - emotion recognition and learning as well as clarifying if sex moderates those associations. For emotion recognition, we found that (i) maltreated youth exhibited reduced recognition of fear, and (ii) that when maltreatment was high, but psychopathology was low, further deficits were observed in recognizing fear, happiness and disgust. These findings supported the latent vulnerability hypothesis for emotion recognition. For emotion learning, no evidence of altered reward or punishment learning, and no latent vulnerability was found in the maltreated groups. We also showed that maltreatment in females was associated with a lower recognition of fear and happiness, whereas maltreatment in males was associated with lower recognition of fear and disgust. Finally, for emotion learning, we showed that maltreated females were poorer at learning from punishment, compared to non-maltreated females, whereas maltreated males showed a reverse pattern (maltreated males made less commission errors than non-maltreated males). Should our findings be replicated in prospective longitudinal studies, they have the potential to clarify if the emotion recognition findings reflect true latent vulnerability and if the reported sex effects translate into males and females developing different forms of psychopathology long-term. They may also prove useful in informing interventions and therapies that target these domains, which have been associated with quality of friendships (Blair et al., 2015), peer and social skills (Germine et al., 2015) in adulthood.

Chapter 4

CHAPTER 4 – AUTONOMIC NERVOUS SYSTEM FUCNTIONING IN MALTREATED YOUTH AS A FUNCTION OF PSYCHOPATHOLOGY

4.1 Introduction

Exposure to adverse experiences in childhood is a risk factor for the emergence of many physical and mental health disorders in adulthood . Research suggests that exposure to early life adversity during this developmental plasticity period may lead to dysfunctions of stress-regulatory systems, increasing the likelihood of developing psychopathological symptoms. In particular, alterations of key regulatory capacities of the autonomic nervous system (ANS) are thought to mediate the association between early adversity and stress-related disorders (Fogelman & Canli, 2019; Gildawie et al., 2021). The ANS regulates involuntary physiological processes and it is divided into the sympathetic (SNS) and the parasympathetic (PNS) nervous systems (Kreibig, 2010). When the SNS is activated, humans enter the 'fight or flight' mode, a state of elevated alertness and attention, in which physiological processes such as heart rate and blood flow increase. When the PNS is activated, a 'rest and digest' process is promoted, by which heart rate and blood pressure are lowered. Thus, appropriate balance between SNS and PNS activation in changing environments is of paramount importance to ensure adaptive functioning (Thayer & Lane, 2000).

Childhood maltreatment (CM), a specific type of early adversity, is defined as abuse or neglect that occurs to children under 18 years of age (Krug et al, 2002). It is a risk factor for a multitude of negative mental and physical health outcomes (Carr et al., 2020; Catale et al., 2020). Growing evidence points towards long-lasting consequences of CM on the structure and functioning of various brain regions working as a network for central autonomic control, such as the anterior cingulate gyrus and the amygdala (Alvarez et al., 2015; McCrory, 2018; McCrory et al., 2017; Teicher et al., 2016a). Studies that examined maltreatment effects on PNS and SNS reactivity have produced mixed findings. For example, some studies reported heightened stress reactivity following CM (Oosterman et al., 2010), while others reported reduced cardiac output reactivity (McLaughlin et al., 2016a), or no association between CM and SNS reactivity (Ellis et al., 2005). In this context, the aim of this study was to assess how childhood maltreatment is associated with the ability to regulate the ANS at rest and during aversive stimuli. Specifically, we were interested in comparing youth with and without maltreatment and examining whether the impact of maltreatment on the ANS differs in youth who develop psychopathological symptoms and those who do not.

One marker of cardiac autonomic regulation is heart rate variability (HRV), which refers to the natural variability in time intervals between succeeding heartbeats over time. HRV is a non-invasive index of PNS activity, which, according to the Neurovisceral Integration Model (Thayer & Lane, 2000), is a marker of vagal inhibition of the heart, reflecting the primary output of the PNS, which is responsible for controlling psychophysiological resources and responses to environmental change (Kemp et al., 2017). This bio-behavioural framework proposes that high HRV is characteristic of a healthy, adaptive system, whereas low resting HRV is associated with poor PNS functioning (Kemp et al., 2017). In the context of CM, however, no consistent association with HRV has yet been identified. Indeed, a recent meta-analysis of 32 studies (N=3652) found no significant association between CM and resting HRV (Sigrist et al., 2021), suggesting that PNS dysregulation caused by CM may only hold true for some individuals (Albott et al., 2018). However, it was noted that both age (i.e., greater reductions in HRV in older participants) and psychopathology (low HRV in clinical populations) acted as moderators of the association between maltreatment and resting HRV. Furthermore, it was highlighted that influential confounding factors such as pubertal status, physical activity and medication need to be better controlled for, as none of the 12 studies including youth samples (out of 32 studies) assessed physical activity levels, and only one study controlled for pubertal development. Taken together, these findings suggest that although there seems to be no association between maltreatment and HRV, i) age and psychopathology might account for this apparent lack of association, and ii) future studies should more thoroughly account for potential confounding variables, such as pubertal status, physical activity, and medication.

SNS activation can be measured using electrodermal activity (EDA), specifically skin conductance level (SCL), which reflects tonic arousal through SNS-controlled changes in the activity of the eccrine sweat gland (Dawson et al., 2011). Lower EDA is associated with a lower arousal, which can be measured during rest or in response to an environmental stimulus. There is a paucity of research on the association between CM and SNS responsivity measured by EDA, with only five studies published to date (Young-Southward, Svelnys, et al., 2020). Carrey and colleagues found that maltreated children showed lower EDA compared to a community sample both across relaxation and laboratory stress (Carrey et al., 1995). Lower EDA was also found when maltreated youth were presented with an anger-inducing conversation in the background while completing a task (Pollak et al., 2005), during a fear conditioning paradigm (McLaughlin et al., 2016a) and during extinction learning, compared to the non-maltreated group (Jenness et al., 2019). In another study, however, no differences in EDA were found between maltreated and non-maltreated children when viewing negative stimuli (Ben-Amitay et al., 2016). Other studies (N=6) using alternative measures of SNS responsivity (e.g., pre-ejection period (PEP), defined as the time between the onset of the left ventricular depolarization and the opening of the aortic valve) show lower SNS activity in maltreated groups. However, this literature is highly heterogeneous, with the majority of studies investigating cumulative adverse experiences (e.g., exposure to natural disasters, being held in captivity) (Heleniak et al., 2016) or exposure to extreme deprivation in youth in lifetime institutional care (McLaughlin, Sheridan, et al., 2015). While these findings seem to indicate blunted SNS reactivity in maltreated youth, the investigated samples were relatively small (e.g., N=11, N=18 in the maltreated groups) and, importantly, none of the above studies controlled for the influence of co-occurring psychopathology.

Substantial research indicates that low resting HRV is associated with a wide range of psychopathological syndromes, such as anxiety, phobias, conduct disorder (CD), and psychopathy (Beauchaine et al., 2007a; Hansen et al., 2007; Neuhaus et al., 2014). According to this extensive line of research, low resting HRV and low reactive HRV to stress mark disrupted self-regulatory functions across various forms of psychopathology (Beauchaine, 2015). Importantly, the recent meta-analysis on the association between maltreatment and resting HRV showed that psychopathology was a significant moderator. That is, when samples were drawn from a clinical population where psychopathology was reported, resting HRV was lower in the maltreated groups (Sigrist et al., 2021). These findings highlight the need to account for the presence of psychopathology, but their generalisability to youth is unclear as only 12 out of 32 studies included in the meta-analysis focused on youth. With regards to the association between psychopathology and SNS activity, meta-analyses have shown that low resting and low stress reactivity EDA are associated with psychopathy, conduct problems (de Looff et al., 2022) and depressive disorders (Sarchiapone et al., 2018). To our knowledge, however, no study has systematically investigated the interactive effects of CM and psychopathology in relation to EDA. Thus, taken together, these findings suggest that while psychopathology might moderate the association between maltreatment and PNS activity measured by HRV, it remains unclear whether the same pattern would be found for the association between maltreatment and SNS activity as measured by EDA. Importantly, examining the interactive effects between CM and psychopathology in relation to ANS functioning could prove crucial in enhancing our understanding of resilience, the ability to function without developing or recovering from psychiatric disorders following periods of adversity (Afifi & MacMillan, 2011). Similarly, this approach provides the opportunity to detect PNS and SNS alterations that could lead to latent vulnerability to psychiatric illness (McCrory, 2018; McCrory et al., 2017). The theory of latent vulnerability proposes that maltreatment is associated with alterations in neurobiological systems which can be supportive of short-term adaptive functioning in threatening environments. In the long term, and in safe environments, however, these alterations confer risk for psychopathology. Thus, by dividing maltreated youth into groups based on the presence or absence of psychopathology, we can examine whether the experience of maltreatment alone is associated with PNS and SNS alterations suggestive of latent vulnerability to poor mental health.

In addition to psychopathology, maltreatment could also have differential effects on the ANS in males and females. Indeed, there is substantial evidence suggesting that the sexes differ in their stress responses (Bangasser & Wiersielis, 2018; Kudielka & Kirschbaum, 2005). In addition, data on healthy individuals have shown that females and males differ in their PNS responses, with females exhibiting higher resting HRV than males (Koenig & Thayer, 2016). With regards to SNS functioning, females have been found to display higher EDA during both relaxation and stress compared to males (Bari, 2020). Relatedly, contrasting sex effects have been observed in the association between externalizing psychopathology and anticipatory EDA responses. Boys with callous-unemotional traits were found to exhibit lower anticipatory fear as measured by EDA (Wang et al., 2012), whereas another study found that girls with CD exhibited reduced EDA discrimination between aversive and neutral stimuli compared to girls without CD (Fairchild et al., 2010). However, despite substantial evidence suggesting that the two sexes differ in their stress responses (Bangasser & Wiersielis, 2018; Kudielka & Kirschbaum, 2005), it is not yet well understood how sex influences the association between maltreatment and ANS functioning.

This study aimed to investigate the main and interactive effects of maltreatment and psychopathology on the PNS and SNS by assessing HRV during a rest period and EDA during a countdown task. Due to high co-occurrence of maltreatment subtypes (Cicchetti & Rogosch, 1997b), we focused on the history of cumulative maltreatment experiences (i.e., including any experience of physical, sexual or psychological abuse or neglect). Moreover, we investigated mental health by combined assessment of psychopathological symptoms (as a dimensional transdiagnostic marker) and the presence of at least one mental disorder, which has been suggested to better describe general psychopathology (Caspi et al., 2014). We divided participants into four groups based on presence/absence of maltreatment and psychopathology and assessed HRV during viewing of a short relaxing video and EDA while participants completed the 'Countdown' task, which involves inducing anticipatory fear. As such, we aimed to investigate psychophysiological correlates of resilience and latent vulnerability by studying youth exposed to maltreatment, but with no form of psychopathology, and explore sex differences in associations between maltreatment and ANS functioning.

i) For PNS activity, we hypothesised that maltreatment *per se* would not be associated with reduced HRV, but that an interaction between maltreatment and psychopathology would be observed such that maltreated youth with low psychopathology would exhibit higher HRV than maltreated youth with high psychopathology (Walker et al., 2017).
ii) For SNS activity, we hypothesised that maltreated youth would exhibit reduced EDA during the countdown task compared to the non-maltreated group – i.e., a main effect of maltreatment.
iii) We also explored whether maltreatment would interact with psychopathology, whereby youth with maltreatment and low psychopathology would exhibit lower EDA compared to the maltreatment and high psychopathology group.
iv) Based on the literature on healthy individuals, we expected to observe sex differences in HRV in the maltreated group. Specifically, we expected maltreated girls to exhibit higher HRV than maltreated boys. Due to the paucity of studies, however, we did not formulate specific hypotheses about sex effects on EDA, nor about interactions with psychopathology.

4.2 Methods

4.2.1 Participants

This study included a subsample of participants aged 9-18 (N=539, 65% females, M age=13.79, SD=2.46) from the FemNAT-CD-study (Freitag et al., 2018). Recruitment took place via community outreach, mental health clinics and youth offending services at 11 different sites around Europe, with a focus on recruitment of females. Participants with an IQ<70 or with a diagnosis of autism spectrum disorder (ASD), schizophrenia, neurological conditions, or genetic syndromes were excluded. Typically developing participants were excluded if they had any psychiatric diagnosis and written informed consent/assent was obtained from all participants and their carers/parents according to site-specific requirements based on age (See Appendix B1 for distribution of participants across data collection sites).

4.2.2 Measures

Psychopathology was assessed using the Child Behaviour Checklist (CBCL) (Achenbach & Ruffle, 2000)) and the Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997a). The CBCL is a checklist completed by parents/caregivers to examine eight dimensions: anxiety/depression, withdrawal, somatic complaints, thought problems, attention problems, rule-breaking behavior, and aggressive behavior. Overall scores were used for analysis, with T scores > 65 used as the clinical cut-off point (Mazefsky et al., 2011). The K-SADS-PL is a clinical interview conducted by trained personnel with the youth and their carers. Presence of psychopathology symptoms in youth was identified based on both these measures (i.e., CBCL scores > 65 and a psychiatric disorder according to the K-SADS-PL). Youth without psychopathological symptoms above the clinical cut-off (as measured by the CBCL) and the K-SADS-PL were allocated to the low psychopathology group.

Participants were divided into four mutually exclusive groups based on measures of childhood maltreatment and levels of psychopathology. Consistent with prior work on maltreatment (Caspi et al., 2002), youth were divided into maltreated and non-maltreated groups using the Children's Bad Experiences Questionnaire (CBE), a 5-item semi-structured interview for parents, caregivers, or guardians to provide information about the child's experiences of physical, psychological, and sexual harm. Specifically, the caregivers responded to standardized probe questions aimed at investigating whether the child/adolescent had experienced i) harm on purpose, ii) harm during discipline, iii) sexual harm, or iv) harm that led to the involvement of an agency (e.g., social services). Examples of probe questions included "Do you remember any time when the child was disciplined severely enough that he or she may have been hurt?" or "Has there been any other situation where your child has been harmed by someone (not accidents)?". Following each discussion, interviewers rated privately the probability that the child had been severely harmed (Lansford et al., 2002). Each rater's judgement (i.e., no/probable/definite maltreatment) was compared with scores from a neutral rater and agreement between the independent raters was reported as 90% (κ = 0.56) in previous studies (Dodge et al., 1995) and in ours. As such, the final groups were as follows: 338 control participants (no maltreatment, low psychopathology; 66.8% females), 18 maltreated participants (maltreatment, low psychopathology; 66.6% females), 99 non-maltreated youth with high psychopathology (59.6% females) and 84 maltreated youth with high psychopathology (65.4% females) (Table 3).

Table 3. Participants' characteristics and psychopathology subscales scores

	Control	**Maltreated**	**High P**	**High P + Maltreatment**	**Group effects**
Sample	N=338	N=18	N= 99	N=84	F/x[2]
Demographic, cognitive, and physical characteristics					
Age, M (SD)	13.7 (2.6)	14.3 (2.5)	13.97(2.2)	14.1 (2.2)	0.9
Females (in %)	66.8	66.6	59.6	65.4	1.8
Estimated Full-scale IQ, M (SD)	105 (11.4) [a]	104.3 (11.4) [a]	95.2 (10.9) [b]	98.8 (12.5) [b]	20.01***
PDS (1=pre/early puberty; 2=mid/late/post puberty) (in %)	2 – 81.9	2 – 94.4	2 – 82.8	2 – 80.9	1.97
SES, M (SD)	0.4 (0.9) [a]	0.5 (0.8) [a]	-0.4 (1.1) [b]	-0.4 (1.1) [b]	33.12***
Use of Medication (in %)	3.8	0	51	42.1	152.52***
Smoking (cigarettes/day), M (SD)	0.45 (2.49) [a]	0.22 (0.94) [a]	5.02 (8.86) [b]	5.02 (7.26) [b]	30.46***

Sports (hours/week), M (SD)	4.47 (4.04) [a]	3.68 (3.12) [a]	3.96 (4.59) [a]	4.1 (5.13) [a]	0.48
BMI, M (SD)	20.33 (3.72) [a,b]	20.20 (2.79) [a]	21.84 (4.7) [b]	21.28 (4.19) [b]	4.15**
Psychopathology subscales scores					
CBCL Total t scores M (SD)	47.79 (8.72) [a]	50.44 (8.84) [a]	74.99 (6.91) [b]	75.06 (5.42) [b]	464.47***
CBCL Internalizing Scale	46.96 (8.51) [a]	49.5 (9.32) [a]	74.96 (6.09) [b]	75 (6.68) [b]	504.95***
CBCL Externalizing Scale	49.81 (8.77) [a]	52.55 (11.36) [a]	69.51 (8.11) [b]	70.76 (7.25) [b]	224.97***
CBCL Anxiety/Depression	53.24 (5.07) [a]	54.88 (5.89) [a]	67.62 (9.67) [b]	70.06 (8.79) [b]	208.58***
CBCL Withdrawal	53.61 (5.44) [a]	56.16 (6.77) [a]	66.59 (8.87) [b]	67.79 (8.92) [b]	155.69***
CBCL Somatic Complaints	55.08 (6.05) [a]	56 (8.21) [a]	65.61 (10.37) [b]	65.67 (9.88) [b]	74.24***
CBCL Social Problems	52.25 (3.92) [a]	52.38 (4.42) [a]	67.4 (9.2) [b]	67.98 (9.56) [b]	239.01***
CBCL Thought Problems	52.41 (4.38) [a]	53.72 (6.07) [a]	67.68 (10.04) [b]	66.77 (9.01) [b]	198.88***
CBCL Attention Problems	52.84 (4.13) [a]	53.33 (3.64) [a]	71.01 (10.25) [b]	71.66 (9.47) [b]	308.85***
CBCL Rule-breaking Behavior	52.35 (4.49) [a]	52.72 (4.02) [a]	73.21 (8.56) [b]	75.58 (8.31) [b]	520.17***
CBCL Aggressive Behavior	52.38 (3.93) [a]	54.22 (5.04) [a]	76.31 (7.98) [b]	75.39 (9.87) [b]	592.11***

Notes: Control = No Maltreatment, Low Psychopathology; Resilient= Probable/Definite Maltreatment, Low Psychopathology; High Psychopathology=No Maltreatment, High Psychopathology; Psychopathology + Maltreatment = High Psychopathology, Probable/Definite Maltreatment; SES = Socioeconomic Status (SES was computed based on parental income, education level and occupation); PDS = Pubertal Developmental Status; CBCL = Child Behavior Checklist; The CBCL scores for the Internalizing scale were computed using the Anxiety/Depression, Withdrawal and Somatic Complaints subscales, whereas the scores for the Externalizing scale were computed using the Rule-breaking and Aggressive Behavior subscales; Post-hoc tests are reported based on observed means, where groups marked with different letters differ significantly from each other at *$p<.05$, **$p<.01$ and ***$p<.001$.

4.2.2.1 Covariates

Pubertal status was assessed using the Pubertal Development Scale (PDS) (Elizabeth B. Robertson,Martie L. Skinner,Margaret M. Love,Glen H. Elder, Jr.,Rand D. Conger,Judith S. Dubas,Anne C. Petersen, 1992) and included in the analysis as a categorical variable with two levels: pre/early puberty versus mid/late/post puberty. IQ was estimated using the Wechsler Intelligence Scales (WASI, WAIS, WISC) (Climie & Rostad, 2011). At the English-speaking sites, IQ was estimated with the vocabulary and matrix reasoning subscales of the WASI-I. Other sites used the vocabulary, block design and matrix reasoning tests of the WISC (for participants aged ≤16) or WAIS (for participants aged 17-18 years). Standardized factor scores for socioeconomic status (SES) were computed based on parental income, education and occupation (Rogers et al., 2019). Other covariates which have been shown to impact the ANS were smoking (i.e., number of cigarettes on an average day), involvement in sports (i.e., number of hours practicing sports in a week), current use of psychotropic medication (e.g., Methylphenidate or Fluoxetine; dichotomous yes/no measure), and body mass index (BMI). Finally, HRV was operationalised by Respiratory Sinus Arrhythmia (RSA), the high-frequency component of HRV, defined as the longest heart period during expiration minus the shortest heart period during inspiration. As respiration rate (RR) can affect RSA independently from PNS activity, this was also included as a covariate when analysing RSA (Hayano, 2004).

4.2.3 Experimental paradigms and dependent variables

4.2.3.1 Assessment of resting HRV - the 5-minute aquatic video

After the electrocardiography (ECG) and impedance cardiography (ICG) electrodes were applied to the participant's body a 10-min habituation period followed. This enabled the participant to become accustomed to the setting to minimize stress induced by the experimental setting. Thereafter a 5-min video (Coral Sea Dreaming, Small World Music Inc.) was presented to obtain the PNS baseline measure. This video appeared effective in promoting PNS resting levels in a previous study (Piferi et al., 2000). The dependent variable was HRV, operationalized by Respiratory Sinus Arrhythmia (RSA). When no difference in shortest and longest beats could be detected, RSA was set to be zero for that breath. RSA values were set as missing when > 50% of the breaths could not be detected or were identified as ‘irregular’.

4.2.3.2 Assessment of EDA - the Countdown task

The Countdown task was designed to elicit responses in anticipation and reaction to an aversive stimulus (Hare & Craigen, 1974). This consisted of the presentation of five aversive loud noises (85dB, duration: 1 sec) (Figure 9). Each noise was preceded by either a *signalled countdown* (numbers counting down from 12 to 1) or an *un-signalled countdown* (a blank screen presented for 12 seconds) to investigate anticipatory fear responding and baseline responding, as measured by EDA. Five bursts of noise were presented. Noises 1, 3, and 5 were preceded by the *signalled countdown*, and noises 2 and 4 were preceded by the *un-signalled countdown*. The 12 seconds following each noise were assessed to investigate the reactive response to the aversive stimuli, resulting in a *signalled response* (response to the announced aversive stimulus) and an *un-signalled response* (response to the unannounced aversive stimulus). This resulted in 3 *signalled countdown* trials, 2 *un-signalled countdown* trials, 3 *signalled response* trials, and 2 *un-signalled response* trials. The dependent variable was the amplitude of the EDA, calculated as the difference in the electrodermal response between the onset and peak of the response during both signalled and unsignalled trials.

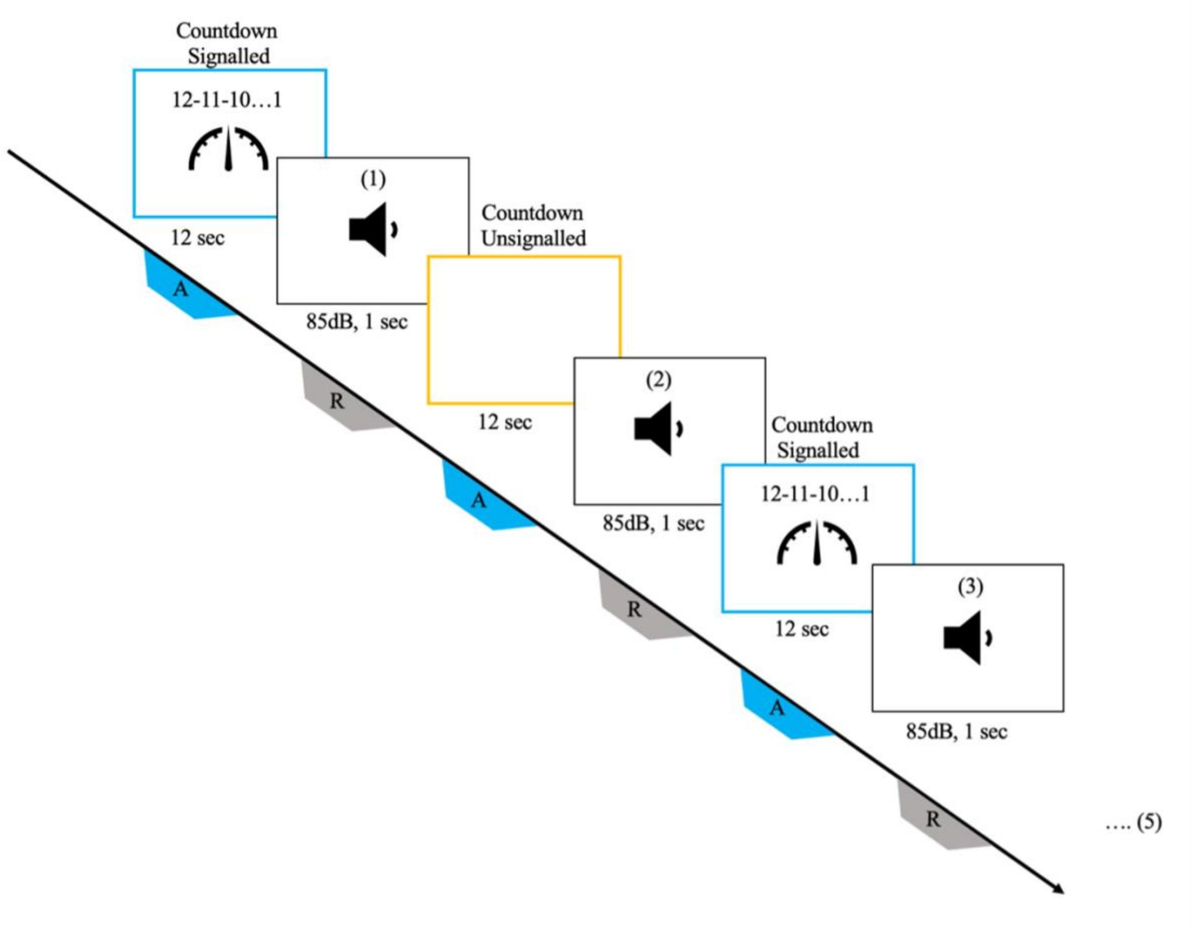


Figure 9. Experimental design of the countdown task.

4.2.3 Procedure

Participants washed their hands with a non-abrasive pH-neutral soap before the electrodes were attached. The physiological assessment started with the 5-minute aquatic video to obtain resting physiological measures. Then, the Countdown task was presented. Participants were asked to sit still and focus on the screen where the following instructions were presented prior to the start of the task: "*In this task you will see numbers* *counting down from 12 to 0. One number will appear every second. When you see the number 0 you will hear a loud noise for 1 s. Sometimes this loud noise will come without any warning, however.*"

4.2.4 Autonomic Nervous System (PNS) recording and pre-processing

Both PNS and SNS measures were collected using the VU-AMS (Vrije Universiteit Ambulatory Monitoring System) device (de Geus et al., 1995). For ECG and ICG measures, two micropore electrodes were attached on participants' back and five on their chest, as described in (Oldenhof et al., 2019). The R-peak time series was derived from the ECG data by an automated detection algorithm within the VU-DAMS software package version 3.9 and was checked manually for missed or incorrect R-wave peaks and abnormalities in the registration. Abnormalities defined as Premature Ventricular Contractions (PVCs) and Premature Atrial Contractions (PACs), or low-quality ECG signal fragments were removed from the data. Ensemble averaged ECG and ICG complexes were derived from all valid heartbeats. In the ensemble averaged ECG, the Q-onset was detected and, in the ensemble, averaged ICG, the B-point (i.e., opening of the aortic valve), dZ/dt-min peaks and X-points (i.e., closing of the aortic valve) were identified by an algorithm within the VU-AMS software package. All scoring in the ensemble averaged complexes was again checked manually. Data on Respiration Rate was derived from the dZ-signal (thorax impedance). 'Irregular respiration' was identified when deviations in the duration of consecutive breaths reached a threshold. When > 50% of the respiration data was identified as 'irregular', respiration rate data was set as missing.

4.2.5 Electrodermal Activity Data Acquisition

For EDA, two Ag-AgCl, non-polarizable electrodes (TSD203, Biopac Systems, Inc., California) were filled with NaCl electrode paste (GEL101, Biopac Systems, Inc.) and attached to the middle phalanx of the middle and index finger of the non-dominant hand of the participant. The VU-AMS device produces a DC measure of electrodermal activity utilizing a 16-bit A/D converter. The signal was sampled at 10 Hz and was measured in micro-Siemens (μS) within a range of 0-95. When EDA was below 1 μS during the complete task, the data were excluded from analyses. The EDA data were pre-processed by a 5th-order low-pass Butterworth filter with a cut-off frequency of 1 Hz using an EDA toolbox (https://github.com/mateusjoffily/EDA/wiki).

4.2.6 Statistical analyses

4.2.6.1 Resting HRV

Before analysis, the RSA measure (the outcome measure for HRV) was checked for outliers. As data distribution was skewed, a base-10 log transformation was applied (Oldenhof et al., 2019) . There were 3 outliers for the RSA, defined as values +/- 3 SD away from the group mean, which were removed from the analysis. To compare HRV between the four groups, we used a 2 (maltreatment: yes/no) by 2 (psychopathology: low/high) by 2 (sex: females/males) design. IQ, SES, pubertal category, medication, smoking, sports, respiration rate, and BMI were regressed from the dependent variable, and standardised residuals were used in the final analysis. (For analyses on two additional PNS and SNS measures, please see Appendix B2).

4.2.6.2 EDA during the Countdown task

To account for the absence of EDA during a trial, magnitudes with a value of zero were added by 1 and data was base-10 log transformed to reach normalization. To compare EDA during the countdown task, we used a 2 (maltreatment: yes/no) by 2 (psychopathology: low/high) by 2 (sex: females/males) by trial (signalled/un-signalled) design for each of the two phases of EDA measurement – anticipation and response to the loud noise. IQ, SES, and pubertal status were included as covariates due to their known association with childhood maltreatment and/or psychopathology (Herrenkohl & Herrenkohl, 2007; Negriff & Trickett, 2010; Young-Southward, Eaton, et al., 2020). Smoking was included as a covariate due to its negative correlation with EDA (Knott, 1984). In line with the HRV analysis, these covariates were regressed from the dependent variable, and EDA standardised residuals were subsequently analysed. Significant interactions were followed by pair-wise *post hoc* comparisons using Bonferroni correction. Effect sizes are reported as partial eta squared (η_p^2) and are interpreted as follows: small ≥0.01; medium≥0.06; large≥0.14 (J. Cohen, 1988).

4.3 Results

4.3.1 Demographic characteristics

The four groups were matched for age, sex, and pubertal status, but control and resilient participants had a higher IQ, higher SES, used no/less medication, and smoked less cigarettes/day than the high psychopathology groups with and without maltreatment (p<.001; Table 3). The control and resilient groups also had a lower BMI compared to the high psychopathology groups (p<.01; Table 3). There were no group differences in psychopathology according to the CBCL subscales scores between the control and resilient groups, and no significant differences between the high psychopathology without maltreatment and the psychopathology with maltreatment groups (Table 3).

4.3.2 PNS Activity – Resting HRV

To test whether maltreatment *per se* was associated with reduced resting HRV, and explore sex differences in PNS functioning, the 2 (maltreatment: no vs. probable/definite) x 2 (psychopathology: low vs. high) x 2 (sex: male vs. female) between groups analysis of variance for RSA indicated a significant interaction between maltreatment and psychopathology. Post-hoc comparisons showed that when psychopathology was low, maltreated youth exhibited a higher HRV (M=0.54, SE=0.29; 95% CI [0.03, 1.12]) than non-maltreated youth (M=0.06, SE=0.07; 95% CI [-0.19, 0.07]) (Figure 10a). When psychopathology was high, the maltreated (M=-0.95, SE=0.13; 95% CI [-0.34, 0.15] and non-maltreated groups (M=0.08, SE=0.12; 95% CI [-0.16, 0.32] did not differ. There were no main effects of psychopathology, maltreatment, or sex on resting HRV values (Table 4).

4.3.3 SNS Activity - EDA during the Countdown task

To test whether maltreatment was associated with reduced EDA and if sex moderated these effects during the response phase (i.e., after the loud noise), the 2 (maltreatment: no vs. probable/definite) x 2 (psychopathology: low vs. high) x 2 (sex: male vs. female) x 2 trial) analysis of variance for the mean EDA amplitude indicated a main effect of maltreatment, where maltreated youth (M=0.21, SE=.12; 95% CI [-0.03, 0.45]) exhibited a higher EDA than non-maltreated youth (M=-0.10, SE=0.06; 95% CI [-0.21, 0.00]) (Figure 10). For the anticipation phase, the analysis revealed that while the main effect of maltreatment was not statistically significant, maltreated youth (M=0.16, SE=.011; 95% CI [0.07, 0.38]) showed the same pattern as in the response phase, exhibiting a higher mean amplitude than the non-maltreated group (M=-0.08, SE=0.05; 95% CI [-0.19, 0.02]). Maltreatment did not interact with psychopathology for this outcome and no main or interactive sex effects were reported by this analysis.

Table 4. Main and interactive effects of maltreatment, psychopathology, and sex on resting HRV and EDA during the countdown task

			HRV - rest		
Main effects	***F***	***df***	***p***	η_p^2	***Post-hoc comparisons***
Maltreatment	1.49	1, 425	.222	.004	-
Psychopathology	2.07	1, 425	.151	.005	-
Sex	0.00	1, 425	.929	.000	-
2-Way Interactions					
Maltreatment by Psychopathology	5.07	1, 425	**.025***	.012	**Low psychopathology**: Maltreated > non-Maltreated **High Psychopathology**: n.s.
Maltreatment by Sex	2.56	1,425	.110	.006	-
Psychopathology by Sex	1.13	1,425	.288	.003	-
3-Way Interactions					
Maltreatment by Psychopathology by Sex	0.09	1,425	.755	.000	-
			EDA - Countdown Task – Anticipation		
Main effects					
Maltreatment	3.74	1, 489	.054	.008	-
Psychopathology	1.94	1,489	.164	.004	-

Sex	1.18	1,489	.277	.002	-
2-Way Interactions					
Maltreatment by Psychopathology	0.00	1,489	.934	.000	-
Maltreatment by Sex	2.55	1,489	.111	.005	-
Psychopathology by Sex	0.06	1,489	.800	.000	-
3-Way Interactions					
Maltreatment by Psychopathology by Sex	0.57	1,458	.451	.001	-

EDA – Countdown Task – Response

Main effects					
Maltreatment	5.34	1,487	**.021***	.011	**Maltreated > non-Maltreated**
Psychopathology	2.14	1, 487	.144	.004	-
Sex	3.23	1, 487	.073	.007	-
2-Way Interactions					
Maltreatment by Psychopathology	0.15	1,487	.692	.000	-
Maltreatment by Sex	1.44	1,487	.231	.003	-
Psychopathology by Sex	1.13	1,487	.288	.002	-
3-Way Interactions					

Maltreatment by Psychopathology by Sex	1.73	1,487	.189	.004	-

Notes: HRV = Heart Rate Variability; EDA = Electrodermal Activity; The adjustment for multiple comparisons were obtained using the Bonferroni correction.

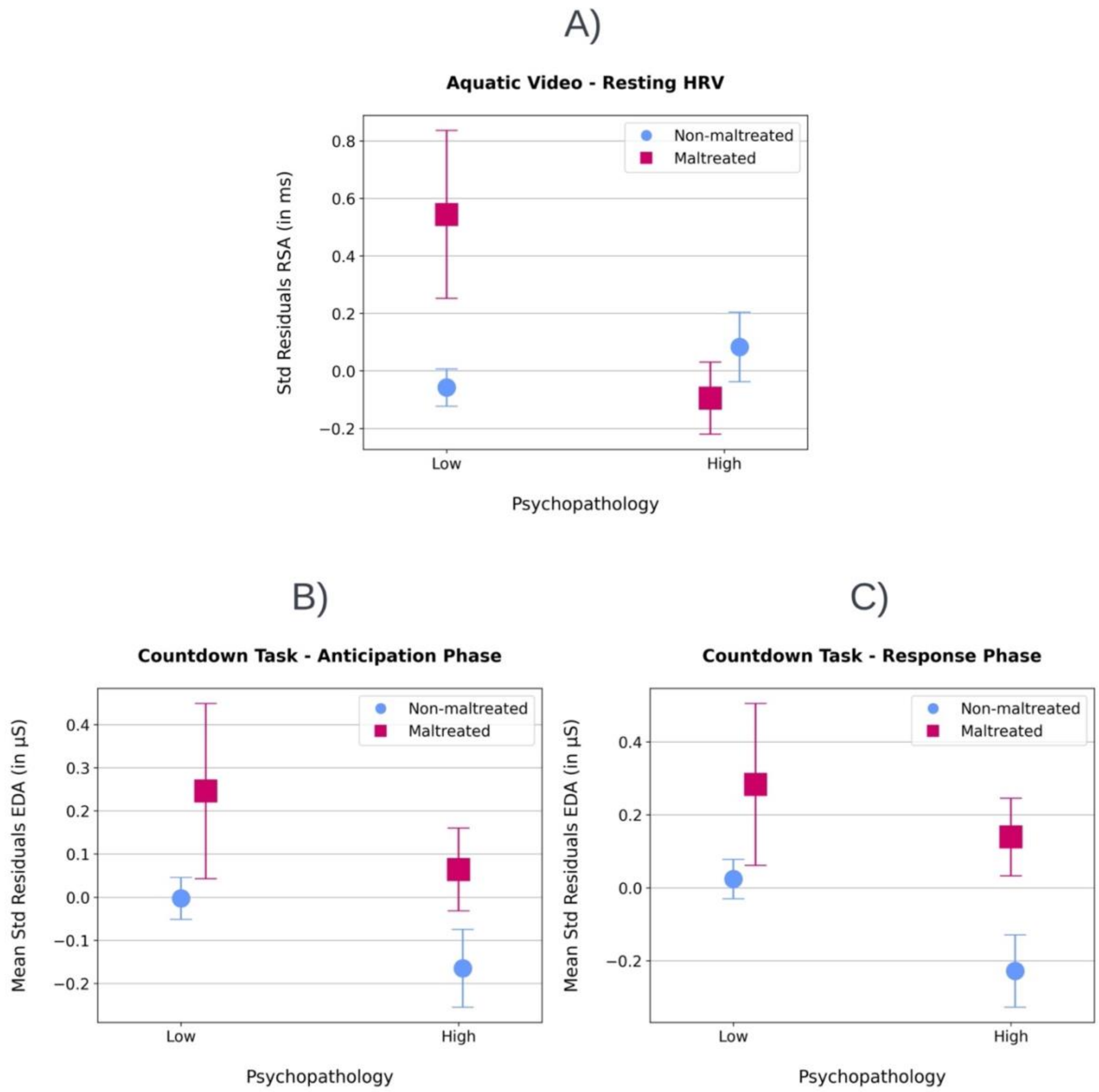


Figure 10. Maltreatment by psychopathology interactions on HRV and EDA.

4.4 Discussion

This study investigated ANS functioning in youth exposed to CM with and without psychopathology to address two aims. First, we wanted to clarify whether maltreated youth exhibit differences in PNS and SNS functioning and to what extent the presence or absence of psychopathology would moderate their responses. For PNS functioning, we hypothesised that maltreated youth's HRV would depend on their levels of psychopathology and that maltreatment *per se* would not be associated with reduced HRV. A significant interaction between maltreatment and psychopathology supported this hypothesis, whereby youth exposed to maltreatment but with low psychopathology showed significantly increased HRV compared to the control group (non-maltreated, low psychopathology). No differences between maltreated and non-maltreated youth were found when psychopathology was high. For SNS functioning, we hypothesised that maltreatment would be associated with reduced EDA during a fear inducing paradigm and expected an interactive effect with psychopathology. Our results, however, did not support this hypothesis and in fact showed the opposite pattern – maltreated youth exhibited higher EDA compared to the non-maltreated group, independently of their psychopathology levels. Second, we investigated whether sex interacted with maltreatment and/or psychopathology to predict PNS and SNS responses. We hypothesised that maltreated girls would exhibit higher HRV than maltreated boys, but this hypothesis was not supported, and no sex differences were found for SNS functioning either. Below we discuss these results considering theoretical and practical implications, as well as further exploratory findings.

In terms of PNS, our finding that, at low levels of psychopathology, maltreated youth showed higher HRV than non-maltreated youth is consistent with findings of a recent meta-analysis where psychopathology was a significant moderator of the association between maltreatment and HRV (i.e., resting HRV was lower in maltreated individuals drawn from clinical population than from non-clinical populations) (Sigrist et al., 2021). Thus, in this context, our findings might reflect a potential psychophysiological correlate of *resilience*. Indeed, according to the Neurovisceral Integration Model, high HRV is characteristic of a healthy, adaptive organism, whereas low resting-state HRV is associated with a vagal impairment (Kemp et al., 2017). Flexibility of the autonomic nervous system at rest is important for adjusting stress responses and it has been suggested that HRV may contribute to individual differences in resilience (An et al., 2020), supporting the view that maintaining parasympathetic dominance at rest may be essential to thrive in the face of adversity. This interpretation is also consistent with previous data showing an association between high HRV and adaptive stress responses (Bornstein & Suess, 2000).

As for SNS, we found that maltreated youth exhibited increased EDA in response to the aversive stimulus and a similar, albeit non-significant effect during noise anticipation. This finding is in contrast with those of a small body of previous studies in youth, which did not control for levels of psychopathology (Carrey et al., 1995; Jenness et al., 2019; McLaughlin et al., 2016a). Our data show the importance of considering both maltreatment and psychopathology and suggest that maltreatment *per se* is associated with a hyperresponsive stress system. While this may initially be adaptive, allowing the child to detect threat in the context of maltreatment and act accordingly, in the long-term and in non-threatening environments, it can become maladaptive and increase the risk for future psychopathology (McCrory, 2018). Indeed, SNS hyperresponsivity has been found to be associated with excessive levels of stress hormones, which may contribute to psychopathology or influence future psychopathology risk (Staufenbiel et al., 2013). Therefore, considered together with the PNS response, the higher EDA found in the maltreated youth shows that while at rest they may exhibit higher HRV indicative of adaptive functioning/resilience depending on their psychopathology levels (i.e., low), when presented with an aversive environment, their hyper-SNS responsivity might in fact reflect *latent vulnerability* (McCrory, 2018).

Importantly, we showed for the first time that maltreated youth exhibited higher EDA during both anticipation (a marginally significant effect, p=.054) and in response to an aversive stimulus (i.e., loud noise) indicative of a hyperresponsive SNS both before and after the noise. First, the higher EDA during anticipation suggests a heightened anticipatory fear, a pattern that contrasts with that found in delinquency-prone adolescents and externalising psychopathologies (Fowles, 2000; Fung et al., 2005; Hare, 1965; MacDougall et al., 2019). It has thus been argued that low anticipatory fear may decrease the fear for negative consequences, which may in turn increase the risk to engage in antisocial behaviours (i.e., *fearlessness theory*) (Raine, 2002). Our results, therefore, suggest that maltreated youth may have a significantly higher fear for negative consequences compared to their non-maltreated counterparts. This finding is consistent with previous research showing that CM is a contributing factor in the overgeneralization of fear in military veterans who have PTSD (Morey et al., 2015). Second, low EDA during the response phase of the countdown task has been interpreted as reduced responsivity to punishment (Hare et al., 1978), hence, we can infer that the high EDA exhibited by maltreated youth after the aversive stimulus may also signal enhanced punishment sensitivity.

On the other hand, recent theories argue that a fundamental difference between maltreated individuals with and without PTSD is a lack of differentiation between safety and threat (Brewin & Holmes, 2003). For instance, one study indicated that adults exposed to childhood interpersonal trauma, failed to show significantly reduced N170 face-sensitive visual ERP component responses to happy relative to angry faces during non-conscious processing (Chu et al., 2016). Trauma exposure was thus associated with a failure to differentiate between positive and threat-related emotion cues. The maltreated group in this study was indeed able to differentiate between safety (indexed by higher resting HRV during the aquatic video) and threat (indexed by higher EDA during the countdown). Given this, we argue that when interpreted together, these findings could also signal an adaptive response in the face of adversity. Overall, our findings corroborate previous literature suggesting that maltreatment alters the learning environment via exposure to extreme affective reactions, yet further investigations would be needed to test these contrasting interpretations (Hanson et al., 2017).

Furthermore, our study did not show a main effect of psychopathology on either HRV, or the electrodermal responses during anticipation or in response to the loud noise. This may be explained by our design, which did not distinguish between internalizing and externalizing subtypes of psychopathology. We therefore ran additional exploratory analyses to investigate resting HRV and EDA during the countdown task as a function of maltreatment, sex, and *internalizing and externalizing psychopathology*, respectively. For HRV, these analyses showed that neither *internalizing* nor *externalizing psychopathology* had a significant main effect on HRV. Moreover, both these subtypes of psychopathology were found to interact with maltreatment to predict resting HRV. Similarly, no main or interactive effects of *internalizing* or *externalizing* symptoms scores were found to predict EDA during the countdown task. (See Appendix B3 for more details). To further explore psychopathology effects on EDA, we divided high psychopathology participants into groups based on presence/absence of Anxiety. This analysis replicated previous literature, whereby youth with high psychopathology and anxiety disorders exhibited higher EDA compared to those with high psychopathology and no anxiety disorders (e.g., OCD, PTSD). More details from this analysis can be found in Appendix B4.

Finally, we did not find any main or interactive effects of sex on either HRV or EDA. Despite evidence suggesting differential stress responses in the two sexes (Bangasser & Wiersielis, 2018; Kudielka &

Kirschbaum, 2005), our findings showed that sex did not moderate the association between maltreatment and PNS and SNS functioning, respectively. This is in line with the meta-analysis investigating early life maltreatment and resting HRV, where sex was not found to be a statistically significant moderator in either the group comparison or correlational meta-regression analyses (Sigrist et al., 2021). Similarly, with regards to EDA, our findings echo previous studies, where, for instance, when youth exposed to maltreatment completed a fear conditioning paradigm, with a loud noise as the unconditioned stimulus, associations of maltreatment with fear conditioning measured by EDA responses did not vary by sex (McLaughlin et al., 2016a). While there is consensus between ours and previous studies, it is important to note that our study may have lacked statistical power, given that the maltreated group with low psychopathology (i.e., the resilient group) was rather small, and only contained six boys. In our previous work with a larger sample, sex differences were indeed reported, where, for instance, maltreated girls showed reduced learning from punishment, and maltreated boys showed better punishment-based learning (Diaconu et al., 2023). As such, future prospective longitudinal studies with bigger sample sizes would be needed to clarify moderating sex effects on the association between maltreatment and PNS and SNS activity.

Several strengths of our study should be highlighted. First, we investigated a large, mixed-sex sample of youth comprehensively assessed for maltreatment and psychopathology. Second, our study is the first to examine main and interactive effects of both maltreatment and psychopathology on PNS and SNS functioning in youth. Third, we used well-established psychophysiology procedures, tasks, and measures. Fourth, our multisite European study extends the generalizability of findings to non-US samples, given that i) the majority of studies included in the meta-analysis investigating HRV in maltreated youth and adults have been conducted in the US (Sigrist et al., 2021) and ii) only one in five studies exploring the association between maltreatment and SNS functioning measured by EDA were conducted in Europe (Ben-Amitay et al., 2016). Fifth, we controlled for several potential confounding variables associated with maltreatment and psychopathology, such as IQ, SES, and pubertal status, as well as those associated with our psychophysiological measures (i.e., BMI, physical activity, smoking, medication, and respiration rate). Nevertheless, our findings should be interpreted in the context of several limitations. First, depending on the sample investigated, (i.e., clinical versus community) and the maltreatment measures employed, the percentage of maltreated youth with no psychopathology can be very small (Cicchetti & Rogosch, 1997b). Whether due to sample characteristics, recruitment strategies, or the definition of resilience used in this study (i.e., absence of any psychopathology as opposed to absence of specific mental health disorders such as PTSD), the resilient group (maltreated, with low psychopathology) was the smallest in our design (N=18). Second, the effect sizes observed in our analyses were small, suggesting that there might be substantial heterogeneity within maltreatment. Third, and relatedly, our maltreatment interview protocol did not distinguish between different subtypes of abuse and neglect, nor were we able to collect information on the onset, severity, or the chronicity of maltreatment. Despite the high co-occurrence of maltreatment subtypes (Cicchetti & Rogosch, 1997b), future studies should make it a priority to investigate these types of adversity separately, as experiences of abuse and neglect have been hypothesised to be associated with different profiles of psychophysiological functioning (McLaughlin, Sheridan, & Lambert, 2014). Fourth, we treated psychopathology as one dimension consistent with evidence for a general psychopathology dimension as a better characterization of mental disorders (i.e., *p* factor, (Caspi et al., 2014)). However, we have addressed the possibility of PNS and SNS responsivity being a function of internalizing and externalizing psychopathology in our supplementary analyses. Importantly, neither of these psychopathology subtypes interacted with any variables to predict resting HRV nor EDA during the countdown task. Finally, the aim of the FemNAT-CD project was to examine sex differences in CD. This means that our high psychopathology groups all met the diagnosis criteria for CD, yet these participants were also characterised by high comorbidity with other disorders (e.g., ADHD (51-52%), ODD (85-87%) (See Appendix B5).

If replicated, our results might also have practical implications for intervention strategies. Heart Rate Variability Biofeedback (HRVB) has been substantially supported as a treatment for a variety of disorders and performance enhancement (Lehrer & Gevirtz, 2014). This procedure consists of feeding back beat by beat heart rate data during slow breathing in order to maximize RSA (Lehrer & Gevirtz, 2014). Moreover, since HRVB involves paying attention to breathing nuances, it works in a similar way to mindfulness and meditation exercises. This interplay between attention regulation and body awareness has been shown to provide more veridical perception, reduce negative affect and improve vitality and coping in both clinical and non-clinical populations (Grossman et al., 2010). Reduced HRV has also been established as a prognostic risk factor for cardiovascular diseases (Rovere et al., 1998). Current models assume that maltreatment increases cardiovascular risk by altering long-term patterns of autonomic regulation characterised by lowered parasympathetic activity. In the context of our study, we can argue that use of this approach in maltreated youth may be highly beneficial to i) potentially protect them from developing psychopathology in adulthood and ii) increase protection against future cardiovascular diseases, one of the leading causes of mortality and morbidity worldwide (Rovere et al., 1998).

To conclude, our study focused on investigating the main and interactive effects of maltreatment and psychopathology on the PNS and the SNS. Specifically, we aimed to disentangle the potentially confounding effects of psychopathology from maltreatment and explore moderating effects of sex. For the PNS, we found that maltreated youth with low psychopathology exhibited higher resting HRV compared to typically developing controls (non-maltreated with low psychopathology). This finding is suggestive of superior autonomic control at rest following maltreatment, which may constitute a key resilience factor. For the SNS, we showed that maltreated youth exhibited higher EDA in response (and a marginally significant effect in anticipation) to an aversive stimulus compared to the non-maltreated group, regardless of psychopathology. These latter results provide evidence of hyper-activation of the SNS in maltreated youth, an alteration that may be indicative of latent vulnerability. However, when interpreted together with PNS functioning (i.e., higher resting HRV in maltreated youth), these findings may also indicate adaptive functioning indexed by the ability to differentiate between safety and threat. No moderating sex effects were found for either the PNS or SNS, suggesting that maltreatment may be associated with similar ANS responses in girls and boys. If replicated in prospective longitudinal studies, our work may prove useful in i) clarifying whether these findings reflect true resilience and/or latent vulnerability and ii) informing therapies that target autonomic and emotion regulation following adversity.

Chapter 5

CHAPTER 5 – CORTICAL AND SUBCORTICAL VOLUME IN MALTREATED CHILDREN. AN ABCD STUDY

5.1 Introduction

Experiences of childhood maltreatment, which include physical/sexual/emotional abuse, and physical/emotional neglect, are associated with cognitive and emotional impairments and are a reliable predictor of negative mental and physical health outcomes (Korbin & Krugman, 2014). These sequalae have been suggested to be (partly) mediated by alterations in brain neurobiology associated with maltreatment, which may increase the risk of developing psychopathology (Hart et al., 2018; Lim et al., 2016; McCrory et al., 2017). Indeed, compared to non-maltreated groups, maltreated individuals have been shown to exhibit alterations in various brain regions, such as the frontal, temporal and parietal regions, as well as anterior cingulate cortex, hippocampus, amygdala, and cerebellum (Calem et al., 2017; Lim et al., 2014; Tymofiyeva et al., 2022; W. Yang et al., 2023). However, the existing research has produced inconsistent findings; For example, some studies suggest reduced volume or cortical thickness in these regions (Lim et al., 2014; McLaughlin et al., 2016a), while others indicate increased volume (Carrion et al., 2009; Whittle et al., 2013). Furthermore, previous studies have not systematically examined the influence of psychopathology and sex on volume alterations in maltreated youth (Tymofiyeva et al., 2022; W. Yang et al., 2023). This study aims to investigate the association between maltreatment and cortical and subcortical volume in children. Specifically, we compared children with and without maltreatment from the ABCD study and investigated how maltreatment is associated with brain volume in the presence and absence of psychopathology, while also exploring sex differences.

Cortical and subcortical volume - the size of brain tissue in the cortex and subcortex – is one of the most prominent neuroanatomical characteristics studied in maltreated individuals (Hakamata et al., 2022). This has been associated with various cognitive, emotional, and behavioural functions (Carrion et al., 2013; Van Harmelen et al., 2010). For example, larger cortical volume, especially in regions involved in executive functions (e.g., the frontal cortex), has been linked to better cognitive abilities, such as attention, planning, and problem-solving. Conversely, reduced cortical volume or thickness in these areas has been associated with cognitive deficits and psychiatric disorders (Bashford-Largo et al., 2022; Mewton et al., 2022; Vythilingam et al., 2002). Findings from earlier studies on brain structural alterations in maltreated children have been highly heterogeneous, with most neuroimaging studies focusing on specific regions of interest (ROIs), such as the hippocampus, and amygdala. For instance, a meta-analysis comprised of 49 studies found that maltreatment was associated with a reduction in hippocampal volume (Riem et al., 2015), while another one including 15 studies found that early life adversity (i.e., maltreatment, poverty, general early life stress) was associated with decreased volume in the hippocampus, but found no differences in amygdala volume (Calem et al., 2017). More recent meta-analyses using a whole-brain voxel-based morphometry (VBM) approach have found *reduced* GMV in the right dorsolateral PFC and right hippocampus (Paquola et al., 2016), but others have also found *increased* volume in the bilateral cerebellum, bilateral middle temporal gyrus, left rostrum of corpus callosum, and bilateral supramarginal gyrus (Tymofiyeva et al., 2022). Importantly, these associations have been found to be moderated by several factors, such as age (Lim et al., 2014; Paquola et al., 2016), sex (i.e., smaller GMV in females) (Paquola et al., 2016) and presence of psychopathology (Calem et al., 2017; Paquola et al., 2016). Specifically, regarding age, Lim and colleagues found smaller postcentral and larger middle occipital GMV were found in older but not younger maltreated individuals (Lim et al., 2014). With regards to psychopathology, (Paquola et al., 2016) found that i) healthy trauma groups exhibited smaller GMV in the dlPFC and postcentral, compared to trauma groups with psychopathology; and that ii) within psychopathology groups, childhood trauma was most strongly associated with reduced GMV in the right hippocampus. By contrast, (Calem et al., 2017),found no association between maltreatment and hippocampal volume when psychopathology was present. Finally, the most recent meta-analysis (Yang et al., 2023) (N= 2550) investigating the effects of childhood maltreatment on cortical thickness and grey matter volume found that maltreated individuals (aged 12-40 years old) exhibited reduced volume in the median cingulate/paracingulate gyri, and the left supplementary motor area (SMA). In line with previous work, it was noted that several structural changes were associated with age (i.e., older individuals showed more alterations in grey matter structure), yet a sub-group meta-analysis for studies in youth exposed to maltreatment was not possible due to inadequate datasets. Moreover, important confounding variables such as socioeconomic status and parental education were not available in most studies. As such, substantial heterogeneity exists in the demographic data included in the analysis.

One significant challenge in understanding the association between maltreatment and brain structure lies in the notable overlap between maltreatment and psychopathology. Indeed, substantial research shows that individuals exposed to childhood maltreatment are at a higher risk of developing both internalising and externalizing disorders, which have themselves been associated with brain structure alterations irrespective of maltreatment history (Barch et al., 2018; Snyder et al., 2017). Specifically, GMV deficits are found in many psychiatric disorders, such as schizophrenia, bipolar disorder, obsessive compulsive disorder (OCD), and anxiety (Goodkind et al., 2015). A study by (Durham et al., 2021) investigating the association between GMV and psychopathology in children from the ABCD study, found that psychopathology as one dimension was inversely associated with GMV in 54 out of 68 cortical regions and in 19 subcortical regions, after controlling for multiple comparisons. Similarly, conduct problems were inversely associated with GMV in 52 cortical regions and 15 subcortical regions, whereas ADHD symptoms were inversely associated with GMV in 25 cortical and 8 subcortical regions. Importantly, the recent meta-analysis on the effects of adversity on brain structure in adults showed that many of the investigated samples had present or past co-morbid disorders that were not accounted for (Yang et al., 2023). Moreover, studies who have accounted for the presence of psychopathological symptoms mainly focused on specific diagnoses such as depression (Yang et al., 2017) or PTSD (De Bellis et al., 2015; Morey et al., 2016). Thus, it is possible that the inconsistencies, both in terms of loci and directions, may partly be associated with co-morbid psychopathology. To identify the distinct associations of maltreatment and psychopathology with brain structures, a potential approach is to categorize individuals who have experienced maltreatment into groups exhibiting psychopathology symptoms versus those without any signs of psychopathology. This approach would facilitate an investigation into whether individuals who have been subjected to childhood maltreatment bear long-lasting effects, rendering them more susceptible, even in the absence of evident psychopathological symptoms. Consistent with the theory of latent vulnerability, a recent framework proposed to explain the link between maltreatment and psychiatric disorders, such approach would also allow us to detect structural alterations that could be associated with future psychopathology (McCrory et al., 2017).

A systematic review (N sMRI studies = 6) (Eaton et al., 2022) of neuroimaging studies investigating resilience following adversity in young people found that adolescents exposed to early adversity (e.g., homelessness, illness, maltreatment) had higher grey matter volumes in the right middle frontal, right superior cortex, and the hippocampus. The direction of the effects on the amygdala, however, remained unclear. (De Bellis et al., 2015) found that maltreated youth without PTSD (i.e., resilient) exhibited *greater* cerebral and cerebellar grey matter volumes than non-maltreated youth. Moreover, a study by (Morey et al., 2016) showed that maltreated youth without PTSD had greater amygdala and hippocampal volume, whereas (Barzilay et al., 2020) found no specific effects of adversity on these two regions. Importantly, the quality of the included studies was mixed, with some not correcting the findings for multiple comparisons (e.g., De Bellis et al., 2015). In addition, some of the reviewed studies investigated the cumulative effect of multiple adversity types, such as deprivation, accidents, or natural disasters, which may have differential effects on brain structure (Teicher & Samson, 2016). Taken together, these findings suggest that the neuroanatomical alterations associated with resilience in children are still poorly understood. Given the significant neural plasticity accompanying childhood experiences, and the link between structural deficits and cognitive and emotional functioning in maltreated adults (Cattaneo et al., 2015), it important to clarify the association between childhood maltreatment and brain structure. In line with our previous work (Diaconu et al., 2023), we examine the main and interactive effects between maltreatment and psychopathology in relation to cortical and subcortical volume to enhance our understanding of the structural brain correlates of resilience (i.e., not developing psychopathological symptoms despite having experienced childhood maltreatment).

In addition, maltreatment can have differential effects on cortical and subcortical volume depending on sex. Research shows that females have lower GMV than males throughout the brain (Gennatas et al., 2017). Specifically, males have been found to have greater GMV than females in the amygdala, thalamus, putamen, and regions known to show reduced volume following maltreatment, such as the temporal and right occipital gyrus (Koolschijn & Crone, 2013; S. Yang et al., 2017). Meta-analyses investigating cortical and subcortical volume in maltreated individuals show mixed findings; (Paquola et al., 2016) found smaller GMV in maltreated females, compared to maltreated males, and Calem et al. (2017) showed that when sex was accounted for, the difference in hippocampal volume was no longer significant between groups with and without childhood adversity. However, (Lim et al., 2014) found no effect of sex on GMV in maltreated children and adolescents, and (Tymofiyeva et al., 2022) could not examine moderating effects of sex due to limited sample sizes. Thus, it is still unclear how maltreatment is related to brain structure in young males and females. For instance, (De Bellis & Keshavan, 2003) showed that maltreated boys with PTSD had smaller cerebral volumes and larger lateral ventricular volumes compared to maltreated girls with PTSD. These findings seem to suggest that maltreatment may have a more profound effect on brain structure in boys. However, as discussed above, it is unclear whether these correlates are linked to experiences of maltreatment or PTSD diagnoses. One of the few studies that investigated sex differences on brain structure in maltreated youth free of psychopathology found that childhood trauma scores in girls were inversely correlated with GMV in regions such as the right prefrontal cortex (PFC), bilateral orbitofrontal cortex, bilateral amygdala, hippocampus, right insula and bilateral cerebellum (Edmiston, 2011). Boys, on the other hand, showed a negative correlation between trauma scores and GMV in the bilateral caudate, tempo-parietal cortex and left-temporo-occipital association cortex. However, this was a study focused on adolescents (aged 12-17 years old), with a small sample size (N= 42), where IQ and SES were not accounted for. Thus, further studies are needed to explore how sex moderates the association between maltreatment and cortical and subcortical volume in children.

This study aimed to investigate main and interactive effects of maltreatment and psychopathology on cortical and subcortical volume in ROIs reported in the latest meta-analysis investigating associations between GMV and maltreatment (Yang et al., 2023) and the systematic review on resilience (Eaton et al., 2022). We focused on studying volume measurements to facilitate comparisons with previous studies that have primarily focused on volume rather than other related metrics such as cortical thickness. To do so, we examined experiences of cumulative subtypes of abuse and neglect, and general psychopathology assessed by combined clinical cut-off scores and presence of at least one psychiatric diagnosis (Caspi et al., 2014). Participants aged 9-10 years old from Wave 1 in the ABCD study were divided into four mutually exclusive groups based on presence/absence of maltreatment and psychopathology. As such, we investigated neuroanatomical correlates of resilience and latent vulnerability by studying children exposed to maltreatment and no psychopathology. Finally, we explored sex differences in the association between maltreatment and brain structure.

Based on the current literature, we hypothesised the following:

i. We expect to replicate findings from (Yang et al., 2023) and find reduced volume in maltreated children in the median cingulate gyri and left supplementary motor area (SMA);

ii. In line with studies in the review by (Eaton et al., 2022), we expect maltreated children without psychopathology (i.e., resilient) to exhibit higher grey matter volumes in the right middle frontal, right superior cortex, cerebellum, and the hippocampus compared to the other three groups. As findings were mixed, we did not formulate a hypothesis about amygdala volume.

iii. Finally, we expect sex to interact with maltreatment and psychopathology. However, given the mixed literature on sex differences on brain structure in maltreated individuals, we did not formulate specific hypotheses regarding the direction of these effects.

5.2 Methods

5.2.1 Participants

This study focused on a subgroup of children aged 9 to 10 years old who were part of Wave 1 (Release 2.0.1) of the Adolescent Brain Cognitive Development (ABCD) study (N=11,877). The imaging data were collected and curated at 21 different sites across the United States (Garavan et al., 2018; Volkow et al., 2018). The ABCD study obtained parental consent and children's assent for participating in the study and the University of Birmingham's institutional review board granted approval for the use of this deidentified dataset. After excluding cases with missing sMRI data (n=2379), the final sample size consisted of N=9,381 participants (49% females). A summary of demographic characteristics can be found in Table 6.

5.2.2 Measures

In line with a recent study examining childhood maltreatment in the ABCD study (Stinson et al., 2021), exposure to physical, sexual and emotional abuse was assessed via the computerised Kiddie Structured Assessment of Affective Disorders and Schizophrenia (K-SADS) for DSM-5 Post-traumatic stress disorder (PTSD) (Kaufman et al., 1997b). Physical and emotional neglect were assessed via the Parental Monitoring Questionnaire (PMQ) (Chilcoat & Anthony, 1996), and the Child Report of Parent Behaviour Inventory (CRPBI) (Schaefer, 1965), respectively. The PMQ is a 5-item measure assessing children’s perceptions of parental knowledge of whereabouts and involvement in day-to day activities. The CRPBI is a 16-item questionnaire which measures youth's assessment of their caregivers' ability to show warmth and provide comfort (See Table 5 for details on scoring items for each maltreatment subtype).

Table 5. Summary of maltreatment measures and their coding

Maltreatment subtype	Measure	Items used	Responses	Coding
Physical abuse	K-SADS for DSM-5 post-traumatic stress disorder (PTSD)	*"Has your child ever been shot, stabbed, or beaten brutally by a non-family member?"* *"Has your child ever been shot, stabbed, or beaten brutally by a grown up in the home?"* *"Has your child ever been beater to the point of having bruises by a grown up in the home?"*	Yes/No	Any "Yes" answer = presence of physical abuse
Sexual abuse	K-SADS for DSM-5 post-traumatic stress disorder (PTSD)	*"A grown up in the home touched your child in their privates, had your child touch their privates, or did other sexual things to your child?"* *"An adult outside your family touched your child in their privates, had your child touch their privates or did other sexual things to your child?"* *"A peer forced your child to do something sexually?"*	Yes/No	Any "Yes" answer = presence of sexual abuse
Emotional abuse	K-SADS for DSM-5 post-traumatic stress disorder (PTSD)	*"A family/non-family member threatened to kill your child?"*	Yes/No	Any "Yes" answer = presence of emotional abuse
Physical neglect	The Parental Monitoring Questionnaire	*"How often do your parents/guardians know where you are?"* *"How often do your parents know who you are with when you are not at school and away from home?"* *"If you are at home when your parents or guardians are not, how*	5-point Likert scale: 1 = "Never" 2 = "Almost never" 3 ="Sometimes" 4="Often" 5 = "Almost always"	Any answer of "Never" or "Almost never" = presence of physical neglect

		often do you know how to get in touch with them?"		
Emotional neglect	Child Report of Parent Behaviour Inventory	*"Makes me feel better after talking over my worries with him/her."* *"Smiles at me very often."* *"Is able to make me feel better when I am upset."* *"Believes in showing his/her love for me."* *"Is easy to talk to."*	3-point Likert scale: 1=Not like them" 2="Somewhat like them" 3="A lot like them"	<u>At least 2 answers</u> of "Not like them" (about the parent or caregiver) = presence of emotional neglect

Presence of psychopathology was assessed using the Child Behaviour Checklist (CBCL) (Achenbach & Ruffle, 2000) and the computerized Schedule for Affective Disorders and Schizophrenia (K-SADS) (Kaufman et al., 1997a). The CBCL is a checklist completed by parents/caregivers to examine eight dimensions: anxiety/depression, withdrawal, somatic complaints, thought problems, attention problems, rule-breaking behavior, and aggressive behavior. Total CBCL t scores > 65 were used as the clinical cut-off point (Mazefsky et al., 2011). In line with our previous work (Diaconu et al., 2023), youth were allocated to the high psychopathology group if psychopathology symptoms were identified based on both CBCL and the K-SADS. Conversely, youth without psychopathological symptoms above the clinical cut-off (as measured by the CBCL) and the K-SADS were allocated to the low psychopathology group.

The final groups were: 8304 control participants (no maltreatment, no psychopathology; 50.8% females), 857 maltreated/resilient participants (with maltreatment, no psychopathology; 40.4% females), 156 non-maltreated youth with psychopathology (31.4% females) and 64 maltreated youth with psychopathology (29.7% females) (Table 6).

5.2.2.1 Demographics

The ABCD Parents' Demographic Survey (PhenX Toolkit) was used to compute a proxy measure of socioeconomic status (SES), based on the level of parental education (Stover et al., 2010). In line with prior studies using ABCD data (Anokhin et al., 2022; Waller et al., 2020; Zhao et al., 2022), cognitive ability was assessed using the composite age corrected scores from the NIH Toolbox Cognition Battery (Picture

Vocabulary, Flanker Inhibitory Control & Attention test, Picture Sequence Memory, Pattern Comparison Processing Speed, Oral Reading Recognition) (Luciana et al., 2018) (Table 7).

5.2.3 Image acquisition

The ABCD Data Analysis and Informatics Center (DAIC) and the ABCD Imaging Acquisition Workgroup collaborated to develop an imaging protocol that ensures consistent data collection on various 3 tesla (3T) scanner platforms, namely Siemens Prisma, General Electric (GE) 750, and Phillips, across 21 data collection sites (Casey, 2018). The protocol involved capturing 3D T1- and T2-weighted images of brain structure. To acquire whole brain T1-weighted images, the following parameters were used: a repetition time (TR) ranging from 2400 to 2500 ms, an echo time (TE) between 2 and 2.9 ms, a field of view (FOV) of 256 × 240 to 256, a FOV phase of 93.75% to 100%, a matrix size of 256 × 256, 176 to 225 slices, an inversion delay (TI) of 1060 ms, a flip angle of 8°, voxel resolution of 1×1×1 mm, and total acquisition times of 7 minutes and 12 seconds for Siemens Prisma, 6 minutes and 9 seconds for GE 750, and 5 minutes and 38 seconds for Phillips.

5.2.4 Data processing and quality assurance

To facilitate centralized processing and analysis of imaging data, DAIC used the Multi-Modal Processing Stream (MMPS), a software package developed and maintained at the Center for Multimodal Imaging and Genetic (CMIG) at the University of California, San Diego (UCSD). The data underwent several pre-processing steps, including the correction of gradient nonlinearity distortions, intensity scaling and homogeneity correction, registration to a standardized reference brain, and manual quality control (QC). Following that, cortical surface reconstruction and subcortical segmentation were conducted using automated, atlas-based procedures in FreeSurfer v.5.3. Morphometric measures were then derived by calculating the average volume in each cortical parcel of the standard FreeSurfer Desikan-Killiany parcellation scheme (Desikan et al., 2006) as well as the average volume in each subcortical region (Fischl et al., 2002). Lastly, trained technicians performed post-processing QC to evaluate motion artifacts, intensity homogeneity, underestimation of white matter, overestimation of pial surface, and magnetic susceptibility artifacts. All brain imaging data analysed in this study (brain volume in mm^3) was thus pre-processed centrally by DAIC. For a more detailed description of the sMRI data acquisition and processing protocol, please refer to (Hagler et al., 2019).

5.2.5 Dependent variables and statistical analyses

5.2.5.1 ROIs analysis

Brain volume in mm^3 was analyzed for ROIs identified in the review on resilience in young people's brain structure (Eaton et al., 2022) and the latest meta-analysis investigating the association between maltreatment and GMV (W. Yang et al., 2023). These were the amygdala, hippocampus, cerebellum, left anterior cingulate cortex, left medial cingulate cortex, paracingulate gyri and left supplementary motor area (SMA). To compare brain volume in each ROI between the four groups, we used a 2 (maltreatment: yes/no) by 2 (psychopathology: yes/no) by 2 (sex: females/males) design. Dependent variables were standardised, and total intracranial volume, cognitive ability and SES were regressed out from GMV. Analysis of variance (ANOVA) was subsequently performed on the standardised residuals, using Pingouin library in Python. Finally, inhomogeneity of variance across groups was accounted for in all the analyses, which corrected for multiple comparisons using the False Discovery Rate (FDR) (Stephens, 2016). Effect sizes are reported using Cohen's D, interpreted as follows: small effect (d = .2), medium effect (d=.5) and large effect (d=.8) (Cohen, 1988).

5.2.5.2 Whole brain exploratory analysis

An additional whole-brain exploratory analysis was conducted to compare whole brain volume in 68 bilateral cortical and 42 subcortical regions. All dependent variables were standardised, and analysis of variance (ANOVA) was performed on standardised residuals, after accounting for total intracranial volume, SES and cognitive ability, with maltreatment (yes/no), psychopathology (yes/no) and sex, as between-subject factors. Like in the ROIs analyses, results were corrected for multiple comparisons using the FDR method (Stephens, 2016).

5.3 Results

5.3.1 Demographics

The control group was slightly older than the maltreated group who was also younger than the high P group. The control group had a higher percentage of females, a higher IQ, and a higher total intracranial volume compared to the other three groups. A summary of the groups' demographics, CBCL total and sub-scores, present KSADS diagnoses and subtypes of maltreatment can be found in Tables 6-7.

Table 6. Participants' demographic characteristics and intracranial volume

	Control	**Maltreated**	**High P**	**High P + Maltreatment**	**F**
Sample	N=8304	N=857	N= 156	N=64	
Age (in months), M (SD)	119.2 (7.5) [a]	117.3 (7.3) [b]	119.23(7.84) [a,c]	118.4 (7.43) [a]	17.41***
Females (in %)	50.75	40.37	31.41	29.68	64.20***
IQ (Age corrected composite score), M (SD)	101.82 (17.44) [a]	94.27 (17.75) [b]	93.82 (18.82) [b]	95.38 (16.45) [b]	59.31***
Intracranial volume (in mm^3), M (SD)	1492464.12 (143187.43) [a]	1471645.23 (146721.21) [b]	1473186.88 (140857.67) [b]	1474223.56 (135916.38) [b]	6.46***
Parental education N (%)					
Less than high school	1140 (13.72)	169 (19.71)	29 (18.58)	10 (15.62)	-
High school	1438 (17.31)	188 (21.93)	34 (21.79)	17 (26.56)	-
Some college	938 (11.65)	133 (15.51)	30 (19.23)	19 (29.68)	-
Bachelor's degree	2438 (29.35)	197 (22.98)	38 (24.35)	13 (21.31)	-
Postgraduate degree	2306 (27.76)	133 (15.51	25 (16.02)	5 (7.81)	-

Table 7. CBCL scores, KSADS diagnoses and maltreatment subtypes by group

	Control	**Maltreated**	**High P**	**High P + Maltreatment**	**F**
CBCL Scores					
CBCL Total t scores M (SD)	43.51 (9.58) [a]	46.03 (9.82) [b]	69.64 (3.51) [c]	70.53 (3.94) [c]	560.09***
CBCL Internalizing Scale	46.65 (9.33) [a]	48.01 (9.77) [b]	68.15 (6.32) [c]	67.31 (7.19) [c]	373.29***
CBCL Externalizing Scale	43.79 (8.79) [a]	45.98 (9.11) [b]	65.24 (7.06) [c]	68.46 (6.71) [c]	475.15***

CBCL Anxiety/Depression	52.41 (4.37) [a]	52.88 (5.01) [b]	66.8 (8.68) [c]	66.35 (9.35) [c]	688.92***
CBCL Withdrawal	52.44 (4.33) [a]	53.56 (5.31) [b]	64.67 (8.75) [c]	64.75 (8.35) [c]	519.6***
CBCL Somatic Complaints	54.19 (5.34) [a]	54.23 (5.54) [a]	64 (7.23) [b]	63.95 (7.92) [b]	220.44***
CBCL Social Problems	51.77 (3.06) [a]	52.73 (3.98) [b]	64.37 (6.64) [c]	64.81 (8.13) [c]	1066.62***
CBCL Thought Problems	52.61 (4.31) [a]	53.44 (5.03) [b]	67.17 (7.22) [c]	67.46 (6.98) [c]	770.54***
CBCL Attention Problems	52.66 (4.32) [a]	54.03 (5.54) [b]	67.59 (9.21) [c]	67.32 (9.71) [c]	747.7***
CBCL Rule-breaking Behavior	51.87 (3.55) [a]	52.81 (4.42) [b]	61.67 (7.91) [c]	65 (7.01) [d]	596.12***
CBCL Aggressive Behavior	51.67 (3.41) [a]	52.24 (3.89) [b]	66.44 (8.03) [c]	70.20 (9.09) [d]	1363.9***
KSADS Diagnoses N (%)					
Bipolar I Disorder	0	0	39 (25)	11 (17.18)	-
Bipolar II Disorder	0	0	15 (9.61)	14 (21.87)	-
Unspecified Bipolar	0	0	13 (8.33)	1 (1.56)	-
Social Anxiety Disorder	0	0	7 (4.48)	4 (6.25)	-
GAD	0	0	10 (6.41)	2 (3.12)	-
Self-harm (no suicidal intent)	0	0	37 (23.71)	16 (25)	-
Suicidal ideation	0	0	55 (35.25)	58 (90.62)	-
Suicidal attempt	0	0	8 (5.12)	4 (6.25)	-
Sleep problems	0	0	67 (42.94)	28 (43.75)	-
Maltreatment subtypes N (%)					
Physical abuse	0	87 (10.15)	0	12 (18.75)	-
Sexual abuse	0	158 (18.43)	0	11 (17.18)	-
Emotional abuse	0	75 (8.75)	0	6 (9.37)	-
Physical neglect	0	592 (69.07)	0	39 (60.93)	-
Emotional neglect	0	148 (17.26)	0	14 (21.87)	-

5.3.2 ROIs

For simplification, we only reported significant results after the FDR correction. The ANOVA only yielded only a main effect of sex ($F(1, 9373) = 14.45$, $p < 0.001$) on volume in the *right* **amygdala,** and *left* ($F(1, 9373) = 18.80$, $p < 0.001$) and *right* **cerebellum** ($F(1, 9373) = 17.38$, $p < 0.001$)**.** Specifically, males exhibited an increased volume in these regions compared to females. No other significant main effects of maltreatment, psychopathology, nor significant interactions between these factors were found on any of the ROIs after the FDR correction.

5.3.3 Whole brain

The analysis of variance on volume in all 68 bilateral cortical and 42 subcortical regions indicated a significant three-way interaction between maltreatment, psychopathology, and sex in the *left* **caudate** ($F(1, 9373) = 11.91$, $p = 0.026$) (Figure 1). |While post hoc comparisons were not statistically significant, data visualisation showed that in the presence of psychopathology, maltreated males (M=0.19, SE=0.15, 95% CI [0.5, -0.10]) had *increased* volume in the caudate compared to non-maltreated males (M=-0.14, SE=0.12, 95% CI [0.09, -0.37], Cohen's d = -0.29). However, when psychopathology was absent, maltreated males (M=-0.16, SE=0.04, 95% CI [-0.00, -0.25]) showed *lower* volume in this region compared to non-maltreated males (M=-0.03, SE=0.01, 95% CI [0.00, -0.06], Cohen's d= 0.13). Maltreated females (M=-0.45, SE=0.21, 95% CI [-0.02, -0.87], on the other hand, showed *decreased* volume in this region compared to non-maltreated females (M=0.20, SE=0.12, 95% CI [0.44, -0.03], Cohen's d= 0.72, when psychopathology was present. When psychopathology was absent, maltreated females (M=0.02, SE=0.05, 95% CI [0.11, -0.08] did not differ from non-maltreated females (M=0.05, SE=0.01, 95% CI [0.07, 0.02], Cohen's d= 0.03). Moreover, significant main effects of sex on cortical and subcortical volume were found, such that males exhibited increased volume compared to females in regions such as the left fusiform, isthmus cingulate, lateral occipital, cerebellum, thalamus, etc.

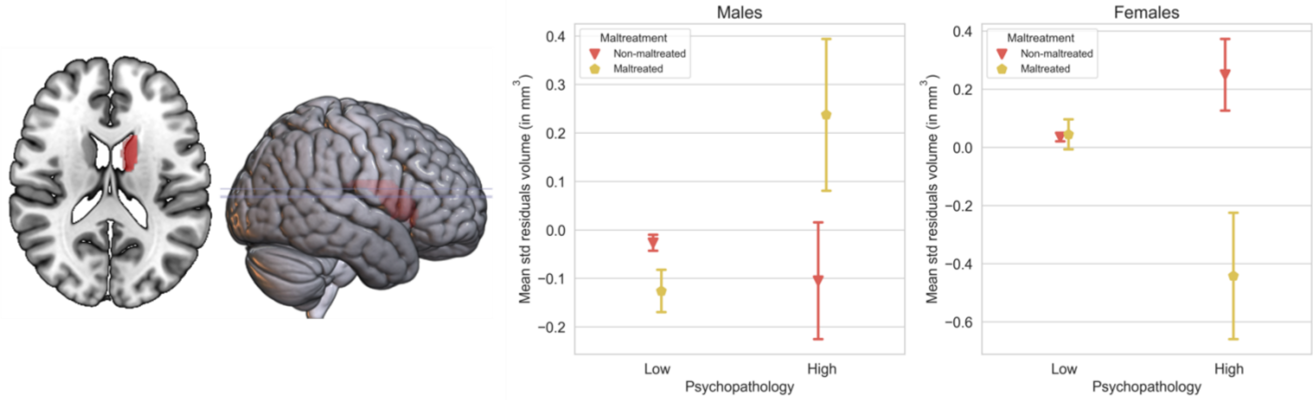


Figure 11. Maltreatment by psychopathology by sex interaction on volume in the caudate nucleus.

5.4 Discussion

This study investigated cortical and subcortical volume in maltreated and non-maltreated children with and without psychopathology from the ABCD study. First, we wanted to clarify whether maltreated children exhibit alterations in brain volume in ROIs previously reported in the literature and investigate the extent to which psychopathology moderated the results. In line with the latest meta-analysis (Yang et al., 2023), we hypothesised that maltreated children would show reduced volume compared to their non-maltreated counterparts, in the median cingulate gyri and left SMA. Our findings did not support this hypothesis. Indeed, maltreatment was not associated with increased or decreased volume in our sample. Moreover, we expected maltreatment to interact with psychopathology to predict brain volume alterations. Specifically, based on the review by (Eaton et al., 2022), we hypothesised that maltreated children without psychopathology (i.e., resilient) would exhibit higher GMV in the right middle frontal, right superior cortex, cerebellum, and the hippocampus compared to the other three groups. Our data did not support this hypothesis either. Finally, however, our exploratory whole brain analysis on 68 bilateral cortical and 42 subcortical regions, indicated a significant three-way interaction between maltreatment, psychopathology, and sex on volume in the caudate. Specifically, in males, maltreatment was associated with increased volume in the presence, but not the absence of psychopathology. In females, the opposite pattern was observed, such that maltreated females exhibited decreased volume compared to non-maltreated females, when psychopathology was present. No differences were found between maltreated and non-maltreated females when psychopathology was absent. However, due to a loss of statistical power and high variance, these differences were not statistically significant for neither males nor females. Below we discuss these results and consider their theoretical and practical implications.

The lack of a significant main effect of maltreatment can be explained by a number of factors. First, it is important to note that the meta-analysis on VBM studies by Yang et al. (2023) revealed reduced GMV in the left SMA and para-hippocampal gyrus in maltreated adults compared to non-maltreated adults, but that subgroups meta-analyses in youth was not possible due to too few datasets. Moreover, it was found that GMV in the left SMA was negatively correlated with average age. Finally, Lim and colleagues found that postcentral and middle occipital GMV alterations were found in older but not in younger maltreated individuals (Lim et al., 2014). Thus, given the young age (9-10 years old) or our sample it is possible that if any structural alterations were to be observed, these would more likely become apparent later in adolescence/beginning of adulthood. Second, as suggested by the SES data of our sample, the ABCD study incudes youth who come from rather affluent backgrounds. Therefore, it is crucial to recognize that the sample in our study differ substantially from the samples commonly investigated in the literature, where participants are sometimes drawn from highly deprived environments (e.g., previous institutionalization, children of alcoholics) (Callaghan et al., 2019; Heitzeg et al., 2008). Finally, the assessment of physical, sexual, and emotional abuse in the ABCD study was conducted using the K-SADS for DSM-5 post-traumatic stress disorder (PTSD), which has been shown to have high concurrent validity and test-retest reliability (Kaufman et al., 1997a). However, for measuring physical and emotional neglect, the Parental Monitoring Questionnaire (Chilcoat & Anthony, 1996) and the Child Report of Parent Behaviour Inventory (Schaefer, 1965) were employed as *proxy* measures. Some items within these measures (e.g., "Smiles at me very often" or "Is easy to talk to,") might not capture more sever forms of maltreatment, which might have reduced/diluted potential associations between maltreatment and brain structures. Hence, our findings suggest that maltreated children aged 9-10 years old do not (yet) show the structural alterations in the median cingulate gyri and left SMA reported in maltreated adults.

Similarly, maltreated children without psychopathology (i.e., resilient) did not show higher GMV in the regions reported in the review investigating resilience in young people's brain structure (Eaton et al., 2022). While the age of the samples included in this review (9-14 years old) is more comparable to ours, most of those studies did not explore sole experiences of maltreatment, but instead focused on a wide range of adversity types, such as exposure to accidents, illness, relocation, or natural disasters (Barzilay et al., 2020;

Burt et al., 2016).Thus, it is possible that we did not replicate those findings due to the more narrow definition of early adversity used in our study. Moreover, the definition of resilience varied across studies. Some classified youth as resilient if they showed low levels of psychopathology and high academic achievement (Burt et al., 2016), while others focused on low mood and anxiety factor scores (Barzilay et al., 2020), or the presence/absence of PTSD (De Bellis et al., 2015; Morey et al., 2016; Sun et al., 2019). Here, our definition of resilience was more stringent, where youth were classified as resilient if they experienced childhood maltreatment, but remained free of *any* form of psychopathology, as measured by below clinical cut-off scores on the CBCL measure, and absence of any K-SADS diagnoses. This design led to 9.13% of our youth to be classified as resilient, compared to approximately 27% in previous studies (Eaton et al., 2022). Clearly, further work is needed to clarify whether the discrepancy between the two sets of finings is related to the younger and more narrow age range of our participants, the heterogeneity of trauma in previous studies, or the exclusion of some versus all psychopathology subtypes.

Interestingly, our whole brain analysis indicated a significant interaction between maltreatment, psychopathology, and sex for the volume of the caudate. This interaction reflected the fact that maltreated males exhibited higher volume compared to non-maltreated males, when psychopathology was present, but an opposite pattern when psychopathology was absent. In contrast, maltreated females showed lower volume of the caudate compared to non-maltreated females when psychopathology was high, but there were no differences between maltreated and non-maltreated females when psychopathology was low. The caudate lies deep inside the brain near the thalamus, forming the striatum, together with the putamen, nucleus accumbens/ventral striatum, and the globus pallidus (Báez-Mendoza & Schultz, 2013). The caudate plays a crucial role in various neurological functions, such as movement execution, learning, memory, reward, motivation, and emotion processing (Fisher et al., 2006; Grahn et al., 2008). A few studies have reported associations between maltreatment and striatal regions, but findings have been inconsistent (Bremner et al., 1997; De Bellis et al., 2002; Kumari et al., 2014; McLaughlin, Sheridan, & Lambert, 2014). For instance, (Cohen et al., 2006) found that adults with no history of psychopathology, and greater than two adverse childhood experiences (ACEs), had smaller caudate volume compared to adults without ACEs. In contrast, (Baker et al., 2013) found that individuals with experiences of early life stress (ELS) in later childhood/adolescence, did not show a significant difference in caudate volume compared to those without ELS. However, our findings are somewhat consistent with a recent mega analysis exploring the interactive effects of childhood maltreatment and depression on cortical and subcortical brain structure (Frodl et al., 2017). Specifically, a significant interaction was found between severity of childhood adversity and sex, such that females exhibited reduced volume in the right and left caudate, but no significant differences were found in males. Moreover, in females, significant negative correlations were observed between all childhood adversity subtypes and caudate volume, and these effects were more pronounced for emotional and physical neglect (Frodl et al., 2017). Last but not least, because maltreated females exhibited reduced caudate volume compared to non-maltreated females when psychopathology was present, our findings complement those by (Cornwell et al., 2023), where it was found that resilience scores negatively correlated with GMV in this area. However, the results reported here also suggest that this pattern may be sex specific. Taken together, our findings suggest that males and females with psychopathology show opposite patterns of structural alterations (i.e., increased versus decreased volume) in the caudate, depending on whether they have experienced maltreatment or not. In line with studies indicating that maltreatment can have differential effects on subcortical volume depending on sex, these findings highlight the importance of examining sex effects when exploring CM-related effects on brain structure (Diaconu et al., 2023).

From a theoretical perspective, our results are consistent with the ecophenotype model, suggesting that maltreatment-related psychopathology might represent distinct ecophenotypes, thus highlighting the importance of considering the influence of maltreatment when examining the neurobiological correlates of different forms of psychopathology (Teicher et al., 2016a). The applicability of this model has been recently tested by (Staginnus et al., 2023), where, for instance, it was found that maltreated youth with CD showed grey matter volume reduction in the right superior temporal gyrus, right prefrontal gyrus surface areas, and lower gyrification in frontal, temporal, and parietal regions compared to non-maltreated youth with CD. Moreover, maltreated youth with CD showed more structural alterations such as lower cortical thickness, volume and gyrification in inferior and middle frontal regions compared to controls (Staginnus et al., 2023). Additional evidence of neurobiological differences between maltreated and non-maltreated individuals with the same diagnosis comes from studies showing reduced hippocampal volume in maltreated individuals with depression, compared to individuals with depression who have not experienced maltreatment (Chaney et al., 2014). Similarly, studies showed that heightened amygdala response to emotional stimuli, a significant factor associated with the development of mood and anxiety disorders, may be exclusive to individuals who have been maltreated (Grant et al., 2011).

Our study has several strengths. First, we used a large, mixed sex, homogeneous sample, with a narrow age range, which enabled us to test the main and interactive effects of our three variables of interest (maltreatment, psychopathology, and sex) whilst limiting the potential influence of developmental differences between our participants (Gerin et al., 2019), as might have been the case in previous studies combining children, adolescents and adults (Riem et al., 2015). Second, we used harmonized analysis protocols, and controlled for important confounding factors, such as IQ, intracranial volume, and SES. Third, we focused on specific types of abuse and neglect, as opposed to broad conceptualizations of traumatic experiences. Finally, our design allowed us to distinguish between experiences of maltreatment and co-occurring psychopathology and explore interactive effects between these factors. As such, we could investigate if maltreated children without psychopathology (i.e., resilient) exhibited brain morphology alterations in ROIs and the whole brain. Similarly, we could also explore whether children with psychopathology differed in brain volume depending on the presence/absence of maltreatment experiences.

Nevertheless, these findings should be interpreted in light of some limitations. By separating maltreatment from psychopathology, our groups were unequal in size. Specifically, the group with maltreatment and psychopathology was the smallest of the four groups (N=64). While our statistical analysis approach accounted for inhomogeneity of variance between groups, it is possible that our design may have lacked the statistical power to detect structural alterations especially when exploring sex effects. Second, we used a cross-sectional design, which impeded us from drawing conclusions regarding the causality of the observed effects. As such, further longitudinal studies would be required to clarify the temporal relation between maltreatment, psychopathology, and brain volume alterations in children. Third, we relied on children's self-reports for experiences of emotional and physical neglect, but used caregivers' reports for physical, sexual, and emotional abuse. This means that low parental endorsements of items where a family member could have been the perpetrator of abuse could not be avoided. Fourth, we did not distinguish between different subtypes of abuse and neglect, nor specific aspects such as onset, duration, or chronicity of the maltreatment. Further research should indeed explore their specific associations with brain volume in maltreated children. Similarly, we did not explore associations with distinct forms of psychopathology. Instead, we explored this as a one-dimensional construct, in line with literature suggesting that mental disorders are best characterised by a general psychopathology dimension (Caspi et al., 2014).

While a vast literature suggests an association between experiences of maltreatment and structural alterations in adults, findings have been inconsistent in children and adolescents. Our study aimed to clarify these inconsistencies by disentangling the potential confounding effects of psychopathology from the effects of maltreatment on brain volume in ROIs previously identified by (Eaton et al., 2022; Yang et al., 2023), and explore potential sex differences. Contrary to our hypotheses, we found that maltreated children aged 9-10 years old did not exhibit significant increases or decreases in brain volume in any of the ROIs previously reported in maltreated adults. Similarly, no significant interactions were found between maltreatment, psychopathology, or sex on either of the ROIs. However, an exploratory whole brain analysis revealed a significant three-way interaction between maltreatment, psychopathology, and sex on the caudate. In males, and in the presence of psychopathology, maltreatment was associated with increased volume, whereas in the absence of psychopathology, the opposite pattern was observed. In females with psychopathology, on the other hand, maltreatment was associated with decreased volume in the caudate, but no differences were observed between maltreated and non-maltreated females when psychopathology was absent. These findings suggest opposite patterns of structural alterations in males and females with psychopathology, depending on the presence/absence of childhood maltreatment, potentially highlighting distinct eco-phenotypes of psychopathology across the two sexes. If replicated in prospective longitudinal studies, these findings could clarify whether volume alterations in maltreated children are only observed in the caudate. Since the caudate has been implicated in neuropsychiatric disorders and emotional regulation (Adamec, 1997; Davidson et al., 1999; Davidson & Irwin, 1999) and is part of the brain dopamine system (Ansorge et al., 2004; Charmandari et al., 2005), clarifying how maltreatment and psychopathology interact to predict the volume of that structure maybe be of paramount importance for implementation of early intervention efforts that may reverse or, at the very least, postpone potential deficits.

Chapter 6

6.1 Summary of findings

In this final chapter, I will provide an overview of findings in Chapters 3-5 (Table 8), discuss their theoretical and practical implications, assess their general strengths and limitations, and provide some suggestions for future research.

Table 8. Summary of findings by chapter

	Chapter 3	Chapter 4	Chapter 5
Domain	Emotion processing – Facial emotion recognition and reward and punishment based learning	ANS functioning - PNS and SNS activity	Brain structure – cortical and subcortical volume
Dataset	FemNAT-CD	FemNAT-CD	ABCD
Sample size	828 (emotion recognition) 717 (emotion learning)	539	9,381
Summary of findings	When psychopathology was low, maltreated youth were less accurate than non-maltreated youth when recognizing happy, fearful, and disgust faces. Both sexes were impaired at recognizing fear; females were also impaired for happy, whereas males for disgust. Maltreated females were worse at learning from punishment compared to non-maltreated females. Maltreated males were better than non-maltreated males.	PNS: When psychopathology was low, maltreated youth had higher HRV than non-maltreated youth. SNS: Maltreated youth exhibited higher EDA than non-maltreated youth irrespective of psychopathology	When psychopathology was high, maltreated males had *increased* volume in the caudate compared to non-maltreated males, whereas maltreated females had *decreased* volume in this region compared to non-maltreated females. When psychopathology was low, maltreated males had *decreased* volume in the caudate compared to non-maltreated males. Maltreated females did not significantly differ from non-maltreated females.

Notes: ANS = Autonomic Nervous System; PNS = Parasympathetic Nervous System; SNS = Sympathetic Nervous System; HRV = Heart Rate Variability (operationalised by Respiratory Sinus Arrhythmia – RSA); EDA = Electrodermal activity.

6.1.1 Chapter 3: Emotion recognition and learning

This work was motivated by evidence of alterations in emotion processing observed in maltreated youth, which has been suggested to indicate latent vulnerability for psychopathology (McCrory et al., 2017), and by inconsistent findings regarding emotion recognition and learning impairments in maltreated youth (da

Silva Ferreira et al., 2014; Leist & Dadds, 2009; Pajer et al., 2010; Shackman & Pollak, 2005). In this Chapter, I showed how maltreated youth exhibited specific alterations in emotion processing depending on the presence/absence of psychopathology and sex. Specifically, for emotion recognition, maltreated youth with low psychopathology were less accurate at recognizing fear, happiness, and disgust compared to non-maltreated youth with low psychopathology. Moreover, a three-way interaction between maltreatment, sex, and emotion type, showed that both sexes were impaired at recognizing fear, but that females were less accurate for happy, whereas males were less accurate for disgust. For emotion learning, maltreated females made more commission errors than non-maltreated females, suggesting an increased difficulty to learn from punishment-based trials. Maltreated males, on the other hand, made fewer commission errors, indicating a superior ability to learn from punishment compared to non-maltreated males. These results were observed independently from psychopathology levels. Finally, our data showed that reward learning was not influenced by neither maltreatment, psychopathology, nor sex.

6.1.2 Chapter 4: SNS and PNS functioning

This chapter was motivated by existing literature indicating altered ANS functioning in maltreated youth (Oosterman et al., 2010), hypothesised to impact mental health, and inconsistent findings regarding the association between maltreatment, PNS (McLaughlin et al., 2016b), and SNS functioning (Carrey et al., 1995), respectively. For PNS, I showed that maltreated youth without psychopathology were better at regulating their autonomic responses at rest, as indicated by increased HRV compared to their non-maltreated counterparts. For SNS, maltreated youth exhibited increased EDA compared to non-maltreated youth, suggesting an association between maltreatment and SNS hyperactivation. These findings were irrespective of the presence/absence of psychopathology. Finally, no main or interactive effects of sex or psychopathology were found on either PNS or SNS activity.

6.1.3 Chapter 5: Brain structure – Cortical and subcortical volume

The motivation for this final empirical chapter came from inconsistent evidence of volume alterations observed in maltreated individuals in specific ROIs, such as frontal, temporal, and parietal regions, the hippocampus, and the amygdala. Our data did not reveal any volume alterations in the previously identified ROIs linked to maltreatment. Instead, a whole brain analysis showed that in the presence of psychopathology, maltreated males had increased volume in the caudate compared to non-maltreated males, whereas females showed the opposite pattern – decreased volume in the caudate compared to non-maltreated females. In the absence of psychopathology, maltreated males showed decreased volume compared to non-maltreated males, while females did not significantly differ from each other.

6.2 Theoretical implications

As highlighted throughout this thesis, the findings reported here highlight the importance of disentangling CM-related alterations from those observed in high psychopathology samples and exploring sex-specific associations. Indeed, a shift has been observed in recent work on childhood trauma, with studies focusing more on symptoms/alterations rather than on diagnoses of PTSD, arguing that this is a more precise avenue of understanding CM (Cay et al., 2022). If replicated in prospective longitudinal studies, the findings reported here have the potential to explain how neurocognitive alterations following CM can increase the risk for psychopathology, and/or promote resilient functioning. For example, recent work by McCrory et al., (2022), showed that altered neurocognitive functioning after CM influences the interactive processes by which people construct their social architecture. Specifically, it has been suggested that individuals with CM are more likely to experience strenuous relationships, and that experiences of abuse and neglect contribute to social thinning, a reduction in the child's support network (McCrory et al., 2022). It is thus possible that like altered threat processing could influence behaviour through hypervigilance or avoidance of threat cues leading to aggressive behaviour or withdrawal, the alterations in emotion processing and learning could also have an impact on social networks (See section 6.4 for more clinical implications of these specific alterations). Moreover, the alterations in PNS functioning exhibited by the maltreated youth without psychopathology provide insight into potential mechanisms of resilience following CM. That is, it is possible that maintaining parasympathetic dominance at rest is a key factor that may protect against psychopathology.

Last but not least, the developmental psychopathology literature has also started to depart from the rigid distinction between psychopathology and typical development, suggesting that the concept of neurodiversity better characterises development (Roccella & Vetri, 2022). It has now been recognised that psychopathology typically emerges as a result of different degrees of alterations in the child's personal, social, and academic functioning, and that exploring this developmental atypia is of paramount importance for our understanding of CM and psychopathology. Such atypia/alterations can provide insights into one's ability to regulate emotional states and organise experiences and behavioural responses. For instance, in the context of neurodevelopmental disorders, the traditional categorical diagnostic system has been suggested to be replaced with a broader umbrella term - ESSENCE: acronym for Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (Gillberg, 2010). The advantage of this approach is that it provides a more accurate picture of clinical reality, especially in the early stages. I suggest that the findings reported here highlight the need for a similar way of defining psychiatric risk following CM (Minnis, 2013), and that a multidimensional approach focused on alterations across various domains is a fruitful start for that conceptual shift. Specifically, by showing that maltreated youth without psychiatric diagnoses can exhibit alterations in neurocognitive domains that may signal latent vulnerability or resilient functioning, and that these may also depend on the sex of the individual, these findings suggest that there is no such strict line between pathology and adaptive functioning. Instead, these findings show that alterations are more likely to be shaped by personal experiences (here, CM), and that these can differ within as well as between individuals (e.g., exhibiting good PNS functioning while resting, but hyperresponsive SNS activity in the presence of aversive stimuli). Thus, taken together, these findings question the conceptualisation of resilience and risk for psychopathology as distinct categories, and highlight a potential coexistence. That is, is it possible for an individual to demonstrate resilience as indexed by a lack of psychopathology, yes still show vulnerability via specific alterations across various domains of functioning. Likewise, it raises the possibility that maltreated individuals with psychiatric diagnoses could also exhibit markers of resilient functioning in certain domains, but not in others.

6.2.1 Latent vulnerability as a preventative approach

Despite a widely recognised link between CM and the elevated risk of psychopathology (Gilbert et al., 2009), our knowledge regarding the neurocognitive alterations associated with latent vulnerability, and the factors contributing to resilience remains limited (Yoon et al., 2021). These gaps pose a significant challenge for clinicians and child protection professionals, as they lack the necessary resources and insights to effectively identify and support individuals who are at greater risk of developing future mental health issues (McCrory, 2018). As posited by the theory of latent vulnerability (McCrory et al., 2017), in this thesis I focused on maltreatment related alterations that may occur prior to the manifestation of psychopathology. If replicated in prospective longitudinal studies, these findings could potentially inform clinical practice.

By using a multi-domain approach, and examining potential alterations in three domains, these findings can assist in shaping a screening tool that clinical practitioners can employ to pinpoint individuals who may be at higher risk of developing psychopathology (Gerin et al., 2019). Specifically, the alterations in fear recognition, and the sex-dependent alterations in happy and disgust recognition identified in Chapter 3, can be considered as markers of latent vulnerability, without signalling overt symptomatology. As discussed in Chapter 3, lower recognition of fear and disgust may indicate an avoidance bias. Although beneficial for a child in a tumultuous or unsafe household, these protective responses may inadvertently reduce the attentional resources allocated to processing other valuable environmental signals. Consequently, this can constrain the capacity for learning and hinder the development of various cognitive and emotional functions (Gerin et al., 2019).

Moreover, the lower recognition of happy faces may be linked to reduced trust or reduced expectations of reward. These alterations could impair the capacity to form positive peer friendships and establish social support systems, which can serve as protective factors against future stressors. Additionally, these alterations may prompt actions that increase the chances of encountering future stressors, such as relationship problems or exclusion from school (McCrory et al., 2002; Gerin et al., 2019). Similarly, the sex dependent alterations in punishment-based learning carry important implications for caregivers, educational settings, and social care professionals, highlighting that different strategies might need to be employed to counteract maltreatment-related behavioural alterations in males and females.

In Chapter 4, maltreated youth showed SNS hyper-activation, an alteration that could also indicate latent vulnerability. Whether interpreted as enhanced punishment sensitivity (Hare et al., 1978) or an enhanced ability to differentiate between safety and threat when considered together with the PNS findings (Porges, 2009), these altered responses following maltreatment are extremely useful to clinicians if they are to be captured before the onset of psychopathology. SNS hyper-activation is linked to dysregulation of emotional processes, usually characterised by strong approach or avoidance emotions, which maintain a wide range of psychopathologies (Beauchaine et al., 2007b). Thus, if prospective longitudinal studies replicate these results, Chapter 4 could also offer clinical practitioners a tool to identify high risk youth. Finally, while in Chapter 5 no markers of latent vulnerability were observed in terms of brain volume, it is important to note that this could be attributed to the relatively young age of the sample. Therefore, it is possible that these changes might manifest in the future, and further research is needed for clarification.

6.3 Implications for resilience

In addition to these proposed markers of latent vulnerability, the novel findings presented in this thesis also highlight important implications for resilience following CM. Indeed, previous work has not considered resilience, latent vulnerability and interactive effects between maltreatment, psychopathology, and sex in these three domains. Specifically, the emotion recognition and learning alterations found in Chapter 3 highlight the complex, dynamic nature of resilience. First, despite an absence of psychopathological symptoms, maltreated youth still exhibited altered neurocognitive profiles, which differed based on sex. These findings are consistent with literature reporting brain changes in maltreated individuals without overt psychopathology (Teicher et al., 2016a; Teicher & Samson, 2016). For example, in a recent study (Ohashi et al., 2019), it was found that both symptomatic and asymptomatic individuals who had experienced maltreatment displayed similar global brain network abnormalities. However, it was possible to differentiate the asymptomatic maltreated (the so called resilient) group from both the symptomatic maltreated group and controls by examining the connectivity patterns of nine specific brain regions. This suggests that maltreated individuals with good mental health are still affected, but may compensate through other neurobiological mechanisms (Cisler & Herringa, 2021; Sun et al., 2019; Teicher et al., 2016a; Teicher & Samson, 2016). This also raises the question of whether we should always consider lack of psychopathology as an index of resilient functioning, without carefully considering other potentially relevant factors, some of which have been included in this thesis (e.g., sex, pubertal timing, SES).

Relatedly, it is also worth noting that for some individuals, what might appear as resilience following CM, may in fact be an indication of unrecognized mental health needs, which may take the form of unhealthy coping mechanisms, increasing the risk of future psychopathology. Indeed, substantial research indicates that a common response following CM is dissociation (Vonderlin et al., 2018), a phenomenon characterised by disruption in the typical integration of consciousness, emotion, memory, perception, and behaviour (DSM 5;

American Psychiatric Association, 2013). Dissociation is seen as a neurobiological mechanism activated in overwhelming situations, when other avoidance systems are not effective (Putnam, 1993). As children and adolescents generally experience a lack of control over caregiver behaviours and environmental circumstances, this hopelessness can make them more vulnerable to dissociative coping (Schauer & Elbert, 2010). Thus, while at one point in time, maltreated youth may seem to function well potentially due to their "detachment" from their traumatic experiences, long term, this coping mechanism can disrupt emotional learning and mental functions, and lead to a variety of mental health disorders. Importantly, this mechanism has also been shown to impede successful psychotherapy of trauma-related psychopathologies (Michelson et al., 1998). Finally, a lack of awareness of mental health needs can also lead to unreported mental health difficulties, and subsequently reduce support seeking behaviours.

Therefore, I propose that beyond the conceptualization of resilience as absence of psychopathology, focusing on the early detection of alterations across multiple domains provides a more comprehensive understanding of the factors that enhance or hinder resilience. The findings in Chapter 4, where maltreated youth with low levels of psychopathology exhibited higher HRV, indicating superior PNS dominance at rest compared to non-maltreated youth, are in line with this approach. However, subsequent assessments over time should be conducted to confirm the contribution of this alteration to resilience. Secondly, even in the absence of any observed alterations, it is essential to emphasize that these conclusions are only applicable to a particular testing moment and to recognize that such alterations may manifest at a different point in time, and vice versa. This observation is particularly important for Chapter 5, where no evidence of alterations in brain volume were found in maltreated youth without psychopathology.

6.4 Implications for clinical practice

If prospective longitudinal studies will show that maltreatment-related alterations are indeed linked to the emergence of psychopathology, a natural next step would be to encourage adaptive change within these systems and identify compensatory protective neurocognitive functions that can enhance resilience (Gerin et al., 2017). This work has then the potential to be the focus of therapeutic interventions. The findings in this thesis enhance our understanding of the neurocognitive effects associated with maltreatment and can assist clinicians and caregivers in reinterpreting the child's conduct and formulating strategies that foster adaptive behaviours. For example, in the context of the emotion processing findings, a crucial factor suggested to promote the re-adjustment of neurocognitive systems altered in maltreated youth is the cultivation of trust (Fonagy & Allison, 2014). Establishing positive, consistent, and secure relationships can potentially alter a child's outlook on others and lay the groundwork for developing trust (Gerin et al., 2019). Such relationships have the potential to re-adjust some of the emotion recognition and punishment-based learning alterations and promote the development of compensatory strategies. This approach would enable maltreated youth to acquire new insights from fresh experiences, reshaping their comprehension of social interactions and personal conduct (Wilson & Sperber, 2012).

Similarly, regarding Chapter 4, resting parasympathetic activity has been suggested to facilitate adaptive responses following loneliness/perceived social isolation. As mentioned in section 6.2, it is not uncommon for maltreated youth to experience hopelessness and perceived isolation following abuse and neglect, and the HRV findings provide important implications for clinical practice. For instance, a recent study by Smith & Pollak (2022) assessed whether resting PNS activity facilitates approach-oriented behaviours in adults, using an approach and avoidance task. It was found that participants with higher resting PNS (i.e., higher HRV operationalised by RSA) and higher levels of loneliness were more likely to approach reinforcers, while those with low PNS activity showed little relationship between approach behaviours and loneliness (K. E. Smith & Pollak, 2022). Importantly, these results remained significant after controlling for age, gender, cognitive ability, and baseline heart rate. These findings suggest that loneliness heightens approach tendencies, but this effect is observed only when other indicators of adaptive responsiveness are present, such as elevated resting PNS activity. Together with the findings in Chapter 4, this indicates that increased resting HRV is a factor that promotes resilient functioning via flexibility, and clinicians could focus on strategies that facilitate PNS dominance in youth with experiences of CM (e.g., HRV biofeedback).

The findings in Chapter 5 suggesting brain volume alterations in the caudate in maltreated youth *with* psychopathology could also have important practical implications if replicated. While no markers of resilience nor latent vulnerability were identified, the main implication of the three-way interaction on caudate volume is that males and females with psychiatric disorders and CM are different from those with psychopathology alone, and the diagnostic nosology might need to recognise this distinction in the future (Teicher et al., 2022).

As discussed in a recent review, this information is crucial when considering treatment planning, when conducting epidemiology and genetic risk studies, and when developing strategies to prevent the emergence of psychopathology (Teicher et al., 2022).

6.5 General strengths

A notable strength of this work is the way in which resilience was investigated. A review by (Stainton et al., 2019) highlighted that the literature is still thorn between different conceptualizations of resilience, with some studies focusing on self-report psychological resilience, while others on resilience to genetic risk. In this thesis, I focused on "observable resilience" measured by the lack of *any* psychiatric diagnoses, but also addressed additional detectable factors that may contribute to or hinder adaptive functioning. This approach is more in line with the complex, dynamic nature of resilience, provides more insights into its underlying mechanisms, and considers important individual differences such as sex. Secondly, all analyses included a control group, which allowed an examination of alterations suggestive of resilience or latent vulnerability in youth who functioned well despite CM, compared to those with low CM exposure and low psychopathology. This means that it was possible ascertain to what extant the other groups' performance differed in their nature and magnitude from 'normal' functioning. Third, by considering the absence of any psychiatric conditions, this work extended prior literature, which mostly focused on alterations related to specific diagnoses, particularly PTSD (De Bellis et al., 2015; Morey et al., 2016; Sun et al., 2019). This is particularly important, as studies show that merely 35% of maltreated children meet diagnostic criteria for PTSD (Famularo et al., 1993). Moreover, maltreated children and adolescents without PTSD exhibit higher rates of anxiety, depression, and externalizing behaviours compared to those with PTSD (Kiser et al., 1993). Last but not least, we used large, mixed sex samples, and controlled for various confounding variable known to be associated with CM and psychopathology.

6.6 General limitations

In spite of these strengths, these findings need to be interpreted considering some limitations. First, all analyses in this thesis used a dichotomous measure of maltreatment (yes versus no); Such design may have failed to consider nuances in alterations linked to maltreatment, specifically between group variation related to different subtypes of maltreatment, severity, onset, and timing. For instance, some evidence suggests that threatening (abuse) versus depriving (neglect) experiences may be related to different brain structure alterations (McLaughlin, Sheridan, & Lambert, 2014). Additionally, it is worth noting that different brain regions exhibit distinct periods of susceptibility throughout development (Andersen et al., 2008; Teicher et al., 2016a) Indeed, some studies have shown that the nature and timing of CM were more strongly predictive of depression (Khan et al., 2015), cortisol levels (Fogelman & Canli, 2018), and inflammation biomarkers (Slopen et al., 2013) than the mere accumulation of CM. Relatedly, it was not possible to account for the CM subtype co-morbidity and repeated exposure, which are likely to be related to further neurocognitive and neurobiological alterations (Green et al., 2000). The significance of comprehending and distinguishing repetitive CM from isolated CM experiences is also highlighted by the recent addition of 'Complex Post-Traumatic Stress Disorder' as a distinct diagnostic category in the ICD-11 (Brewin, 2020). Similarly, nuances in alterations may also have been lost because of investigating general psychopathology, as opposed to distinct psychiatric diagnoses.

6.6.1 Cultural and racial differences

In addition, this work has not explored cultural differences in alterations in the three investigated domains. For instance, studies on the universality of emotion recognition (Ekman et al., 1987) have faced criticism, suggesting that they underestimate cultural differences by employing tasks with forced-choice responses and contrived facial expressions (Russell, 1994). Indeed, one study (Izard, 1971) showed that while the emotion recognition accuracy of most groups was significantly above chance level, European and American participants tended to achieve higher scores when using American expressions compared to their Asian or African counterparts. Similarly, in another study, Ethiopian participants accurately recognised the six universal emotions only 52% of the time, compared to 83% for American participants (Ducci, Arcuri, W/Georgis, and Sineshaw, 1982). Thus, whether cultural differences in emotion recognition exist due to display or decoding rules (Matsumoto, 1992a), language (Mesquita et al., 1997), or an in-group advantage (Markham & Wang, 1996), future work should try to investigate whether culture interacts with experiences of CM to predict emotion recognition alterations. Moreover, cultural differences exist in the use of physical punishment, which are associated with more aggression among European Americans as opposed to African Americans (A. B. Smith, 2006). Given this, it seems reasonable to hypothesise that cultural differences may exist in punishment-based learning. That is, it is possible that some CM exposed youth learn associations of punishments more slowly/faster than others depending on culturally ingrained stimulus-response associations.

Similarly, regarding ANS functioning, recent evidence suggests that race may be linked to differences in SNS activity (Chong et al., 2023). While the relationship between race and culture has been a source of debate, with race being considered a biological construct, some research shows that there is more within- rather than between-group variation in races (Winker, 2004). This observation has prompted researchers to conceptualize race as a social construct, closely intertwined with culture. Despite this ongoing debate, it is crucial to note that racial differences may exist in psychophysiological responses, and future work should make it a priority to consider them. For instance, it has been suggested that racial differences in SNS activity may be attributed to factors such as lifestyle, genetic differences, psychosocial effects of race in the lab, or psychosocial environmental factors (e.g., racism, self-stereotyping, etc) (Chong et al., 2023). More specifically, differences in EDA among racial groups have been proposed to be linked to factors like skin hydration, skin colour, and the number of sweat glands (Chong et al., 2023). For instance, Black participants tend to exhibit higher levels of trans-epidermal water loss and lower skin hydration compared to White participants (Wan et al., 2014). In turn, skin hydration can influence skin conductivity levels, as the amount of water content directly correlates with electrical conductivity (Davies et al., 2017). Race may also be a prominent factor for differences in PNS functioning. A study by (Hill et al., 2017), showed that lifelong subjection to racial discrimination, and discrimination in the form of threats and aggression, inversely predicts HRV in African American individuals. Other studies showed diminished PNS activity among African American populations, specifically among obese African American women, compared to non-Hispanic white participants (Farrell et al., 2020).

Finally, neuroimaging studies have also shown brain structural differences between Eastern and Western cultures. (Tang et al., 2018) found that male Chinese participants displayed increased brain volume and greater cortical thickness in the temporal cortex and cingulate regions, whereas male Caucasians exhibited larger brain volume and cortical thickness in the frontal and parietal regions. Kochunov et al. (2003) compared East Asian adults who spoke Chinese and Caucasian adults who spoke English, reporting greater volume in the frontal, temporal, and parietal regions among Chinese individuals compared to Americans. They suggested that these differences could be attributed to the linguistic characteristics associated with the practice of speaking Chinese (Kochunov et al., 2003). This contrast between independent (i.e., Western), and interdependent cultures (i.e., East Asian, including Taiwan, Japan, Korea and China) has gained particular attention in the recent literature, with more studies emphasising the need to consider the generalization of findings from western, educated, industrial, rich, and democratic (WEIRD) samples to non-Western samples (Henrich et al., 2010). One example of studies that could address these sample characteristic differences is the prospective longitudinal 1993 Pelotas study, which recruited over 5,000 new-borns (99.7% of all births) in the city of Pelotas, Brazil (Reichert et al., 2009). Another is the Consortium on Vulnerability to Externalizing Disorders and Addictions (c-VEDA), which recruited a cohort of 10,000 6-23 years across seven Indian sites, with the aim of examining environmental influences on genes, neurodevelopmental trajectories and vulnerability to psychopathology, with a focus on externalizing disorders (The cVEDA Consortium et al., 2020). Thus, taken together, these findings highlight the importance of considering cultural and racial differences in emotion processing, ANS functioning, and brain structure. Importantly, they also emphasize the need for future research to explore how culture interacts with CM experiences to predict alterations in these domains, and whether these findings are replicated in non-WEIRD samples.

6.7 Secondary data analysis challenges

All data analysed in this thesis were collected as part of larger cohort studies, namely FemNAT-CD and the ABCD study. This choice was motivated by numerous advantages, such as large sample sizes, enhanced data quality due to standardised procedures, higher representativeness of the general population (ABCD), and optimized use of resources (Tripathy, 2013). However, despite these benefits, there are a few challenges that need to be considered. The initial data collection was not conducted with the aim of addressing the research questions of this thesis. This poses some limitations to the analyses. For example, the FemNAT-CD consortium was aimed at exploring sex differences in CD (Freitag et al., 2018). This means that all youth classified as high psychopathology had a diagnosis of CD, a specific type of externalizing psychopathology. While supplementary analyses accounted for differences between internalizing and externalizing problems, and the psychopathology group had other co-morbid diagnoses, this sample characteristic remains important when interpreting the findings in Chapter 3 and 4. Similarly, the ABCD study was aimed at exploring brain development and child health in the US (Volkow et al., 2018). Although valid and reliable instruments have been employed to explore various forms of abuse (i.e., K-SADS; Kaufman et al., 1997), proxy measures were used for the assessments for different types of neglect (Chilcoat & Anthony, 1996; Schaefer, 1965). Thus, it is possible that the threshold for abuse may have been stricter than the one for neglect, and future work using more direct measures of neglect would be needed to replicate the findings in Chapter 5. Second, analysing secondary data often means that access to some information regarding data collection, such as low response rates or participant misunderstandings while completing the tasks may be limited. For instance, in the FemNAT-CD, information on computation of missing data is provided (Eekhout et al., 2014), but no details are available on the percentages of that transformed data. Therefore, constraints stemming from the data's original purposes, potential differences in abuse and neglect thresholds, and limited access to certain information about data collection, emphasize the need for caution in interpreting the findings in this thesis.

6.8 Suggestions for future work

There is scope for future research to advance our understanding of CM related alterations by opting for more intricate designs that consider the potentially mediating and moderating factors mentioned in section 6.6. Indeed, there is now a range of statistical techniques available for exploring the intricacies of these interactions (Ioannidis et al., 2020). These methods can help map an individual's trajectory following CM experiences by using known initial condition parameters. For example, when investigating complex resilience/latent vulnerability factors within large datasets, future research may consider employing structural equation modelling (SEM). SEM is a comprehensive approach that encompasses path analysis (an extension of regression analysis) and latent variables. This technique is well-suited to examine hypotheses related to mediation and moderation, providing insights into the mechanisms of resilience and psychiatric risk, and the conditions governing the strength of those linking mechanisms (Ioannidis et al., 2020). Second, the cross-sectional design did not allow for a quantification of change in alterations over time. Prospective longitudinal designs, along with more versatile statistical techniques such as latent growth curve modelling, would be of paramount importance for establishing causation. As well as being suitable to examine resilient functioning and latent vulnerability trajectories over time, this technique could also reduce measurement errors (deRoon-Cassini et al., 2010). Finally, to study heterogeneity between youth with experiences of different types of abuse and neglect, future work may opt for normative modelling (Marquand et al., 2019). This is an analytical approach that involves identifying patterns, trends, and variations within the data, and defining typical/expected characteristics. Specifically, it employs a statistical model to link variables (e.g., demographic, behavioural) to quantitative measurements (e.g., a brain read-out), and calculates centiles of variation within the population (Wolfers et al., 2020). As a result, it enables individuals to be positioned within a standard range, quantifying both the centiles of variation within the cohort and the deviation of each individual from the group mean. For instance, (Loreto et al., 2022) applied this technique to study neuroimaging profile variation in Alzheimer's disease (AD), by including clinical feature such as disease severity, presenting phenotypes, and comorbidities. It was found that the superior temporal sulcus was the region with the highest number of outliers (60%) in AD patients, followed by the temporal (31.5%) and extratemporal regions (19.1%). Finally, heterogeneity in CM-related alterations could also be explored via machine learning techniques. These approaches operate with minimal assumptions and have the capacity to extract structured insights from large datasets, which can effectively shape personalized approaches in the prevention and treatment of mental health conditions (Bzdok & Meyer-Lindenberg, 2018). By integrating data from various sources, such as neurocognitive and neurobiological data, into a predictive model, it would be possible to explore profiles of CM-related alterations, as well as pathways and underlying markers or latent vulnerability and resilience (Griffiths et al., 2022). Applying these techniques to investigate heterogeneity in CM-related alterations could be an important avenue for CM research.

6.9 Summary and conclusions

In summary, the findings in this thesis highlight alterations related to CM on emotion recognition and learning, ANS functioning, and brain volume. Importantly, some of these alterations depended on the absence/presence of psychopathology and the sex of the individual, highlighting the importance of accounting for comorbid psychopathology and sex effects. These findings can be interpreted considering the theory of latent vulnerability, and provide insights into protective factors that may contribute to resilience following CM. This knowledge may also aid clinicians in early intervention and support strategies (H. Walker et al., 2013). However, there are several factors that still need to be investigated. Future studies should address the heterogeneity in alterations between different subtypes of maltreatment over time and consider cultural and racial differences. By employing more complex statistical techniques, and prospective longitudinal designs, such studies would allow us to better understand the mechanisms of resilience and psychiatric risk following CM. Overall, this thesis provided novel data CM-related alterations in neurocognitive and neurobiological domains and underscored the importance of early detection and intervention to support maltreated youth.

A.1 Distribution of participants

Table A9. Distribution of participants per group, sex, and site.

Site	**Total** *N*	**Control$_f$** *n*	**Control$_m$** *n*	**Resilient$_f$** *n*	**Resilient$_m$** *n*	**PT$_f$** *n*	**PT$_m$** *n*	**MT+PT$_f$** *n*	**MT+PT$_m$** *n*
Aachen	251	65	57	8	4	37	32	25	23
Frankfurt	194	77	54	3	4	11	18	14	13
Birmingham	92	46	31	3	0	2	6	1	3
Athens	84	44	16	3	0	8	6	5	2
Bilbao	66	32	10	2	0	13	2	6	3
Southampton	39	18	16	1	0	0	4	0	0
Barcelona	33	13	0	0	0	10	4	4	1
Basel	29	22	0	2	0	4	0	1	0
Szeged	27	10	3	0	0	7	2	4	1
Amsterdam	12	0	0	0	0	8	0	4	0
Dublin	2	1	1	0	0	0	0	0	0
	828	**328**	**188**	**22**	**8**	**100**	**72**	**64**	**46**

Notes: $_{f/m}$=female/male; Control = No Psychopathology, No Maltreatment; Resilient = Probable/Definite Maltreatment only; PT= High Psychopathology only; MT+PT=Probable/Definite Maltreatment, and High Psychopathology.

A.2 Inclusion criteria

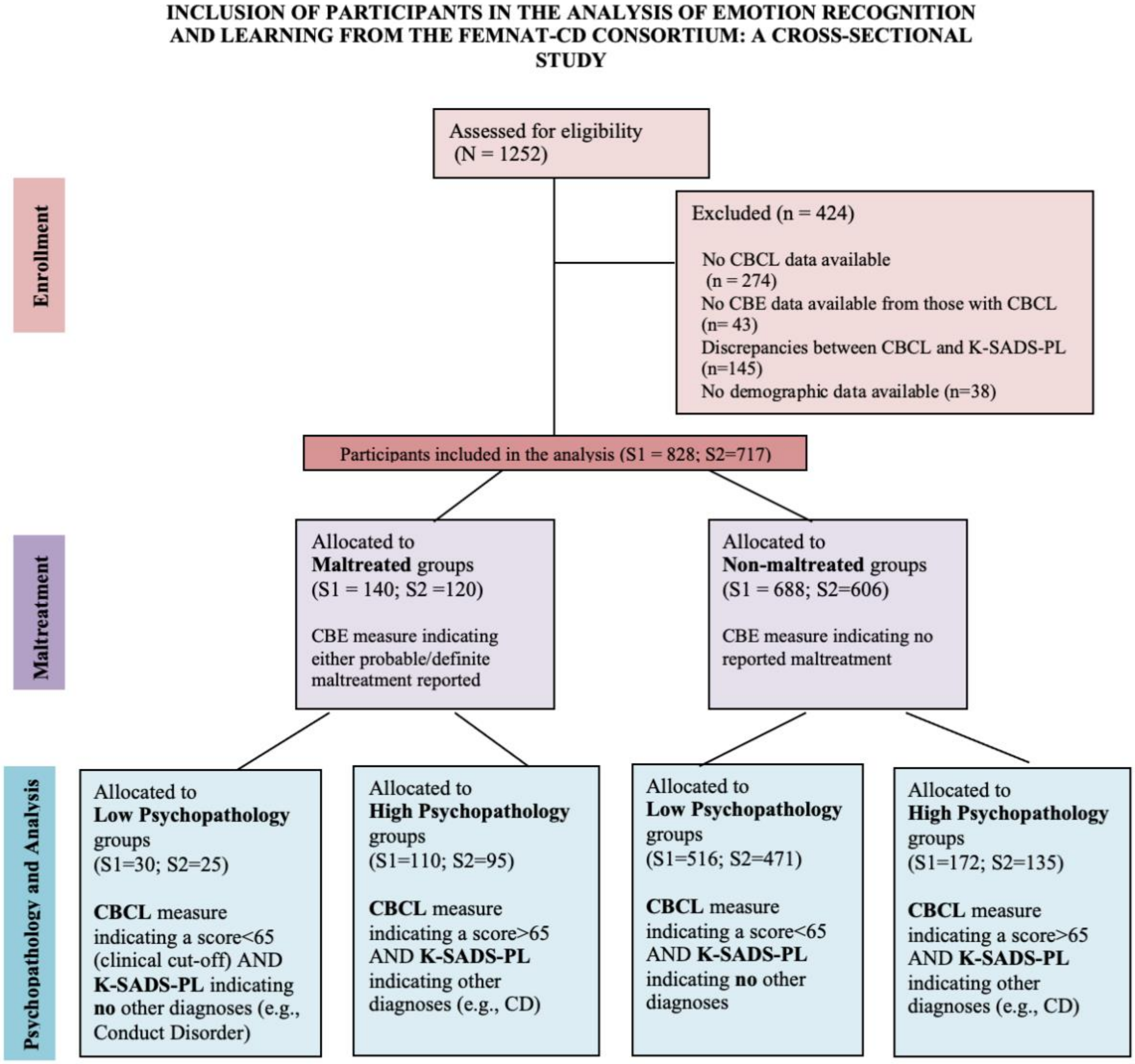


Figure A12. Participants' inclusion criteria

A.3 Participants' characteristics in the emotion learning sample

Table A10. Participants' demographic characteristics and psychopathology subscales scores. The Passive Avoidance sample.

		Control	Resilient	High Psychopathology	Psychopathology + Maltreatment	Group effects
Sample	**Study 2**	**N=471[2]**	**N=25[2]**	**N=135[2]**	**N=95[2]**	
Age, M (SD)		13.71 (2.5)	14.2 (2.4)	14.2 (2.4)	14.03(2.4)	0.9
Females (in %)		66.1	76.6	58.8	50.6	5.8
Estimated IQ, M (SD)		107.1 (10.7) [a]	103.1 (10.5) [a]	96.4 (10.2) [b]	96.7 (13.8) [b]	12.7***
Estimated Verbal IQ, M (SD)		105.6 (13.2) [a]	102.6 (14.2) [a]	96.8 (14.6) [b]	93 (17.6) [b]	21.4***
Estimated Performance IQ, M (SD)		105 (13.1) [a]	102.6 (14.2) [a]	96.8 (14.6) [b]	102.1 (14.2) [a]	7.8***
PDS (1=pre/early puberty; 2=mid/late/post puberty) (in %)		2 – 82.4	2 - 80	2 – 81.1	2 – 84.6	0.1
SES M (SD)		0.4 (0.9) [a]	0 (1.1) [a]	-0.3 (1) [b]	-0.5 (1.1) [b]	21.8***
CBCL Total t scores M (SD)		48.2 (8.2) [a]	51.6 (6.9) [a]	75.5 (7.2) [b]	76.3 (6.1) [b]	442.6***
CBCL Internalising Scale		47.6 (7.9) [a]	50.6 (7.5) [a]	75.8 (6.2) [b]	76.6 (5.9) [b]	508.7***
CBCL Externalising Scale		49.8 (8.2) [a]	53.2 (6.9) [a]	69.3 (8.9) [b]	71.1 (9.0) [b]	198.2***
CBCL Anxiety/Depression		53.2 (4.8) [a]	53.6 (4.9) [a]	68.4 (10.3) [b]	71.2 (9.2) [b]	204.9***
CBCL Withdrawal		53.6 (5.2) [a]	55 (5.7) [a]	67.1 (9.8) [b]	68.8 (9.7) [b]	145.5***
CBCL Somatic Complaints		54.6 (5.8) [a]	58.2 (7) [a]	65.5 (10.7) [b]	65.5 (11.5) [b]	66.7***
CBCL Social Problems		52.5 (4.6) [a]	54.5 (4.1) [a]	69 (9.5) [b]	69.6 (9.4) [b]	233.2***
CBCL Thought Problems		52.2 (4.4) [a]	53.6 (5.1) [a]	67.8 (10.2) [b]	67.3 (10.9) [b]	176.5***
CBCL Attention Problems		52.7 (5.2) [a]	53.6 (4.1) [a]	72.7 (8.9) [b]	75 (10.5) [b]	333.2***
CBCL Rule-breaking Behaviour		52.3 (4.3) [a]	53.6 (4.2) [a]	74.9 (8.6) [b]	77.2 (7.6)	578.7***
CBCL Aggressive Behaviour		52.3 (3.8) [a]	53.5 (3.9) [a]	77.3 (8.6) [b]	77.5 (9.4) [b]	626.4***

Notes: Control = No Maltreatment, Low Psychopathology; Resilient= Probable/Definite Maltreatment, Low Psychopathology; High Psychopathology=No Maltreatment, High Psychopathology; Psychopathology + Maltreatment = High Psychopathology, Probable/Definite Maltreatment; SES = Socioeconomic Status (SES was computed based on parental income, education level and occupation); CD = Conduct Disorder (Diagnosis of CD was based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Lifetime and Current versions (KSADS-L/C); PDS = Pubertal Developmental Status; CBCL = Child Behaviour Checklist; The CBCL scores for the Internalising scale were computed using the Anxiety/Depression, Withdrawal and Somatic Complaints subscales, whereas the scores for the Externalising scale were computed using the Rule-breaking and Aggressive Behaviour subscales; EMM = Estimated Marginal Mean; SEM = Standard Error of the Mean; Post-hoc tests are reported based on observed means, where groups marked with different letter differ significantly from each other at *p<.05, **p<.01 and ***p<.001.

A.4 Inter-rater reliability

Inter-rater reliability (IRR) values were calculated for comorbid disorders, notably ADHD), MDD, ODD and GAD (Cohen's kappas >= 0.84 and agreement across trained raters >= 92% for all diagnostic categories). The severity of CD and comorbid disorders was defined based on the number of symptoms endorsed across informants (i.e. a symptom was considered present if endorsed by either informant). The inter-rater reliability was conducted on a subsample of participants (n=75) from across all of the FemNAT-CD research sites. For ethical reasons, at the UK sites two interviewers attended the sames interviews but coded the interviews seperately; at all other sites, interviews were videotaped and scored by different raters.

A.5 Task randomization

Participants completed a neuropsychological test battery comprised of the Emotional Hexagon Task, the Passive Avoidance Learning Task and the Emotional Go/No Go Task (not included in this study). Each clinical site was provided with a "Permutation List" for the computerized test battery including the different task orders. Task order was randomized separately for age (i.e., 9-12 yrs., 13-15 yrs., and 16-18 yrs.), group (i.e., Psychopathology/Conduct Disorder (CD) and Typically Developed Controls (TDC)) and gender (i.e., female, male). Permutation number of task order (1 to 6) was noted and entered into the online database. Tasks were randomized according to the following scheme:"

Female cases, age 9-12 years Page No[i]. |____|

<table>
<tr><th>Study-ID</th><th>Subject-ID for Computer tests[ii]</th><th>Permutation No.</th><th>Test/Task 1</th><th>Test/Task 2</th><th>Test/Task 3</th><th>First Video Clip</th></tr>
<tr><td>01-|_|_|_|_|</td><td>|_|_|_|_|_|</td><td>1</td><td>Hexagon</td><td>Go/Nogo</td><td>Avoidance</td><td>bear</td></tr>
<tr><td>01-|_|_|_|_|</td><td>|_|_|_|_|_|</td><td>2</td><td>Hexagon</td><td>Avoidance</td><td>Go/Nogo</td><td>champ</td></tr>
<tr><td>01-|_|_|_|_|</td><td>|_|_|_|_|_|</td><td>3</td><td>Go/Nogo</td><td>Hexagon</td><td>Avoidance</td><td>bear</td></tr>
<tr><td>01-|_|_|_|_|</td><td>|_|_|_|_|_|</td><td>4</td><td>Go/Nogo</td><td>Avoidance</td><td>Hexagon</td><td>champ</td></tr>
<tr><td>01-|_|_|_|_|</td><td>|_|_|_|_|_|</td><td>5</td><td>Avoidance</td><td>Hexagon</td><td>Go/Nogo</td><td>bear</td></tr>
<tr><td>01-|_|_|_|_|</td><td>|_|_|_|_|_|</td><td>6</td><td>Avoidance</td><td>Go/Nogo</td><td>Hexagon</td><td>champ</td></tr>
<tr><td>6-digit Study-ID</td><td>5-digit Subject-ID for Neuropsych. Testing</td><td></td><td colspan="3"><---------- Randomized Task order ----------></td><td></td></tr>
</table>

Figure A13. Example of Permutation List with Study-ID, Subject-ID and the six possible task orders

A.6 Emotion recognition and learning results by largest data collection sites

The FemNAT-CD is a multi-site study and to account for potential confounds related to participants being tested at different European locations, we have re-run the analyses by only including the sites with the biggest numbers of participants (i.e., Germany and UK, N= 576). For emotion recognition, the analysis of covariance showed main effects of psychopathology, sex, emotion and morph. There were also significant interactions between emotion and sex, and emotion, psychopathology and maltreatment. These results are in line with the ones reported in the main manuscript, where data from all 11 sites were analyzed. However, there were also some discrepancies, in that the emotion by maltreatment interaction was no longer significant (p=.072), and neither the emotion by sex by maltreatment (.055). For emotion learning, re-running the analysis with these two sites only, resulted in the same pattern of results. For avoidance errors, we found main effects of psychopathology, sex and block, two-way interactions between sex and maltreatment and sex and psychopathology, and the same sex by maltreatment by block, and sex by psychopathology by block (Table A11).

Table A11. Main and interactive effects of CM, psychopathology and sex on emotion recognition and learning (UK + Germany sites)

			Emotion Recognition		
Main effects	***F***	***df***	***p***	η_p^2	***Post-hoc comparisons***
Maltreatment	1.24	1, 562	.266	.002	-
Psychopathology	6.5	1, 562	.011	.011	-
Sex	17.64	1, 562	*p*<.001	.030	-
Emotion	19.64	5, 2810	*p*<.001	.034	Happiness > Surprise = Sadness > Anger > Fear > Disgust (All emotions differed significantly at p<.001 level, except from Surprise vs. Sadness (*p*>.05)
Morph	7.98	1, 562	.005	.014	-
2-Way Interactions					
Emotion by Maltreatment	1.86	5, 562	.172	.000	-
3-Way Interactions					
Emotion by Maltreatment by Psychopathology	5.5	5, 562	.019	.010	Low Psychopathology: **Happiness, Fear, Disgust**: Maltreated < Non-Maltreated Anger, Surprise, Sadness: n.s.

					High Psychopathology: n.s.
Emotion by Sex by Maltreatment	2.16	5, 4040	.055	.004	-

Emotion Learning

Main effects	*F*	*df*	*p*	η_p^2	*Post-hoc comparisons*
Psychopathology	8.17	1, 498	.004	.016	-
Sex	5.53	1, 498	.019	.011	-
2-Way Interactions					
Sex by Maltreatment	5.58	1, 498	.018	.011	Maltreated Females > Maltreated Males Non-Maltreated: n.s.
Sex by Psychopathology	4.09	1, 498	.043	.008	Low Psychopathology: Females > Males High Psychopathology: n.s.

Notes: Covariates evaluated in the model were SES = 0.125, mean-centred IQ=1.245, and pubertal status (1 = pre/early puberty; 2 = mid/late/post puberty). The adjustment for multiple comparisons was obtained using the Bonferroni correction.

A.7 Pubertal category and age effects

Table A12. Pubertal category effects in the emotion recognition and emotion learning analyses.

Emotion Recognition

Main effects	*F*	*df*	*p*	η_p^2	*Post-hoc comparisons*
Pubertal category	35.14	1, 808	*p*<.001	.042	Post >Pre

Emotion Learning

Main effects	*F*	*df*	*p*	η_p^2	*Post-hoc comparisons*

Pubertal category	8.43	1, 707	.004	.012	Post>Pre

Notes: Covariates evaluated in the model were SES = 0.125, mean-centred IQ=1.245, and pubertal status (1 = pre/early puberty; 2 = mid/late/post puberty). The adjustment for multiple comparisons was obtained using the Bonferroni correction.

Table A13. Main and interactive effects of maltreatment, psychopathology and sex on emotion recognition and learning *with age replacing pubertal category as a covariate*.

Emotion Recognition

Main effects	***F***	***df***	***p***	η_p^2	***Post-hoc comparisons***
Maltreatment	5.31	1, 817	.021	.006	MT < nMT
Psychopathology	3.84	1, 817	.05	.005	High < Low
Sex	26.70	1, 817	$p<.001$	.032	Females > Males
Covariates					
Age	119.87	1,817	$p<.001$	.128	-
SES	23.73	1,817	$p<.001$	.028	-
IQ	30.35	1,817	$p<.001$	.036	-
2-Way Interactions					
Emotion by Maltreatment	2.52	5, 4085	.027	.002	**Fear:** MT < nMT Anger, Happiness, Surprise, Sadness, Disgust: n.s.
Emotion by Age	6.17	5, 4085	$p<.001$	.008	-
Emotion by SES	4.24	5, 4085	$p<.001$	.005	-
Emotion by IQ	2.4	5, 4085	.035	.003	-
3-Way Interactions					
Emotion by Maltreatment by Psychopathology	2.22	5, 4085	.049	.010	Low Psychopathology: n.s. High Psychopathology: n.s.

Emotion by Sex by Maltreatment	3.01	5, 4085	.01	.002	MT comparisons: n.s. Between Sex comparisons: No Maltreatment: **Females > Males (Fear, Disgust)** Maltreatment: **Females > Males (Disgust)**

Emotion Learning

Main effects	***F***	***df***	***p***	η_p^2	***Post-hoc comparisons***
Psychopathology	7.89	1, 715	.005	.011	High < Low
Sex	4.69	1, 715	.031	.007	Females > Males
2-Way Interactions					
Sex by Maltreatment	5.17	1, 715	.023	.007	n.s.
Sex by Psychopathology	4.5	1, 715	.034	.006	Males: High Psychopathology> Low Psychopathology Females: n.s.

Notes: Covariates evaluated in the model were SES = 0.125, mean-centred IQ=1.245, and pubertal status (1 = pre/early puberty; 2 = mid/late/post puberty). The adjustment for multiple comparisons was obtained using the Bonferroni correction.

A.8 Age by emotion interactions

We have further explored the significant interaction between age and emotion. Consistent with previous literature, recognition accuracy improved with age for all emotions except happiness. For descriptive purposes, we have now included graphs showing the % recognition accuracy for each of the six emotions, in each of the ten age groups (9y old to 18 y old). For ease of interpretation, we have divided these age groups into 2 age categories (i.e., Category 1 = 9 to 13 years old; Category 2 = 14 to 18 years old) and ran a 2 (age category) by 6 (emotions) analysis of variance. This analysis highlighted the same pattern of results, in that there was a main effect of age category (F(1,826)=69.82, p<.001, $\eta_p{}^2$=.078; 2>1), which also significantly interacted with all emotions, except happiness (F(5,4130)=5.62, p<.001, $\eta_p{}^2$=.007).

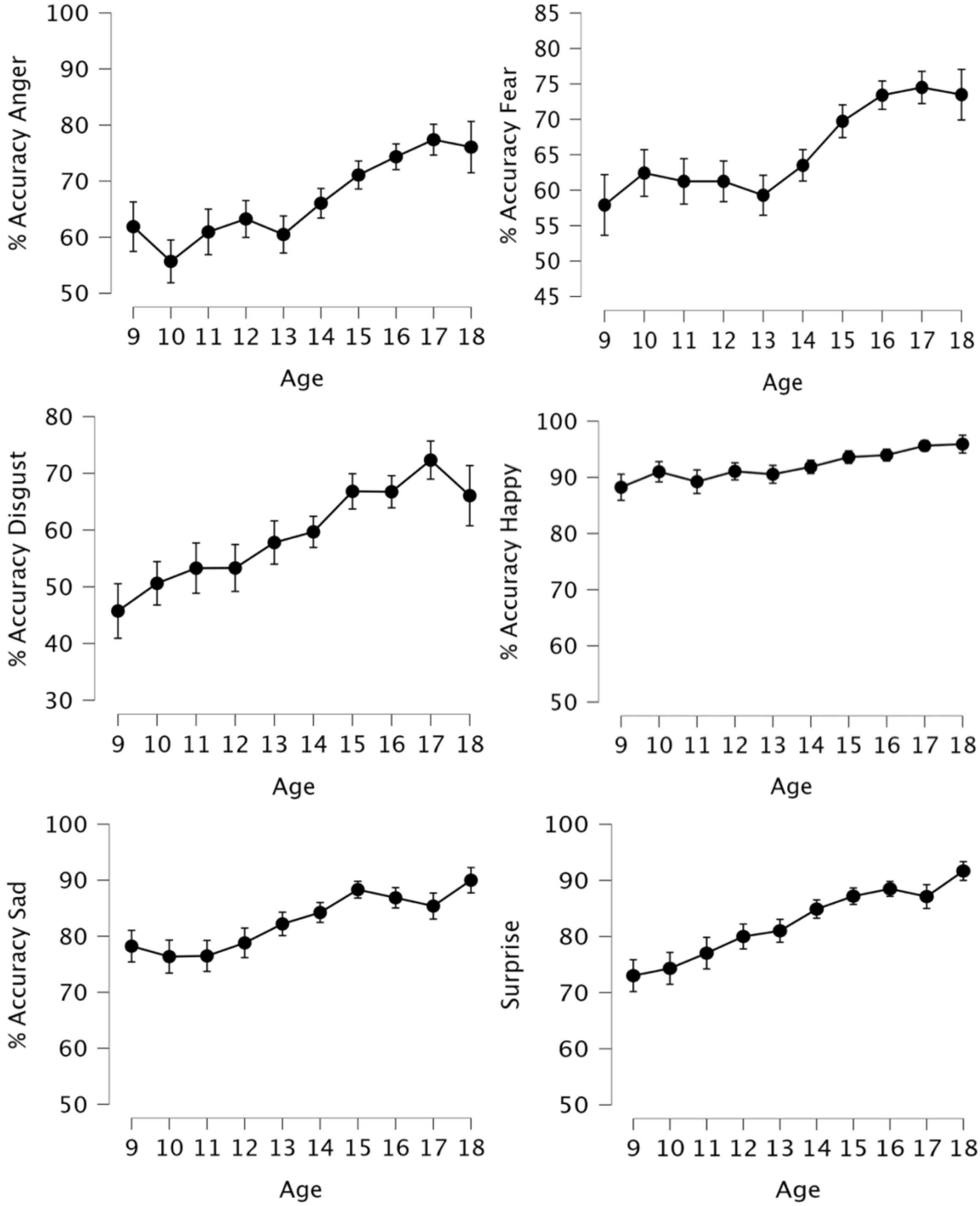


Figure A14. Emotion by age groups interaction in the Emotion Hexagon task.

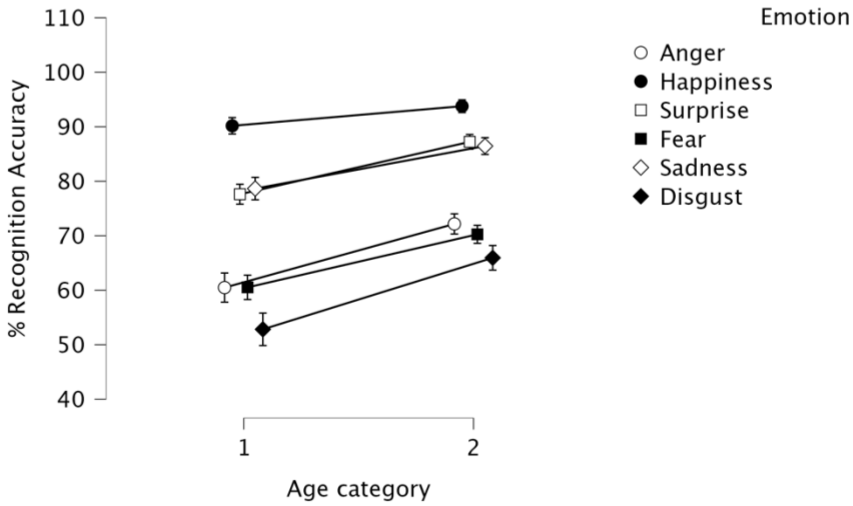


Figure A15. Emotion by age category interaction in the Emotion Hexagon task.

A.9 Emotion recognition results in females

Table A14. Main and interactive effects of CM and psychopathology on emotion recognition. Female sample only.

Emotion Recognition					
Main effects	***F***	***df***	***p***	η_p^2	***Post-hoc comparisons***
Maltreatment	1.62	1, 507	.204	.003	nMT > MT
Psychopathology	8.35	1, 507	.004	.016	Low > High
Covariates					
Pubertal category	24.98	1,507	*p*<.001	.047	-
SES	10.01	1,507	.002	.028	-
IQ	9.1	1,507	.003	.018	-
2-Way Interactions					
Emotion by Maltreatment	2.28	5, 2535	.044	.004	n.s.
3-Way Interactions					

Emotion by Maltreatment by Psychopathology	0.87	5, 2535	>.05	.002	-

Notes: Covariates evaluated in the model were SES = 0.125, mean-centred IQ=1.245, and pubertal status (1 = pre/early puberty; 2 = mid/late/post puberty). The adjustment for multiple comparisons was obtained using the Bonferroni correction.

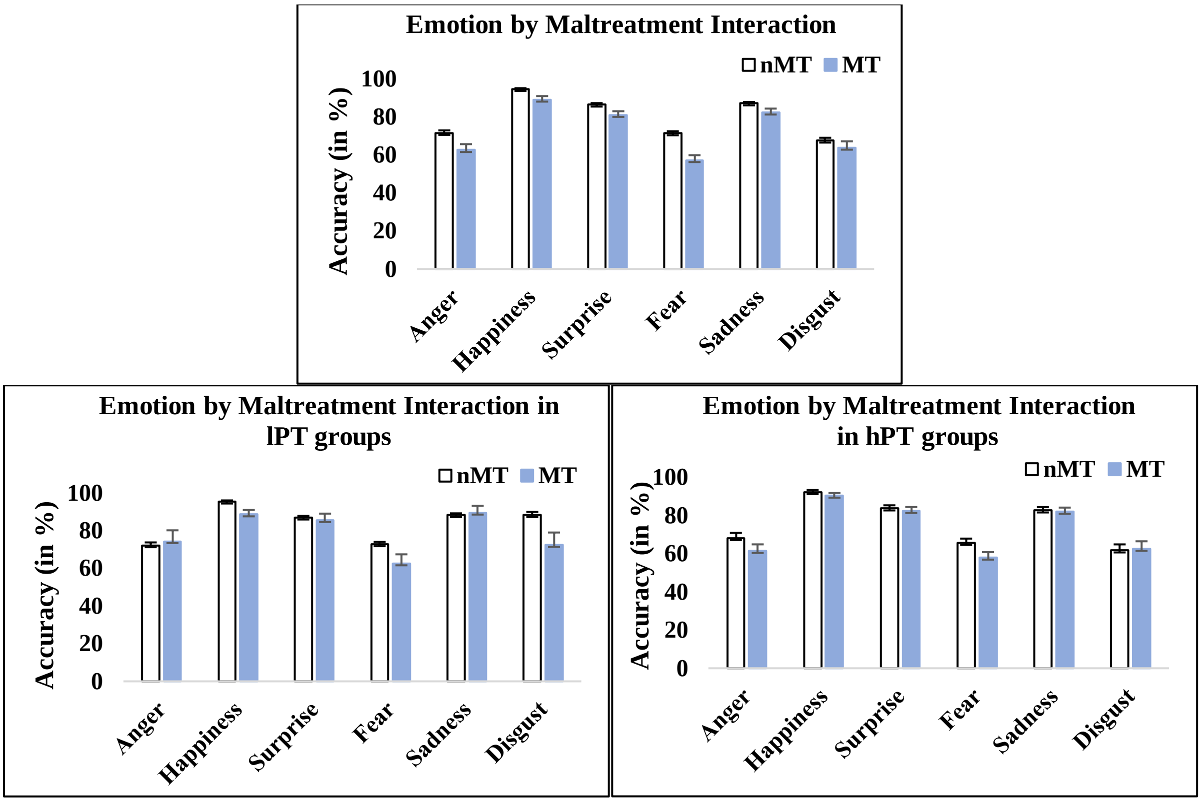


Figure A16. Interactions between emotion, maltreatment, and psychopathology in the female sample

A.10 The Passive Avoidance Learning task. Results by block

In the passive Avoidance Learning task, participants completed 10 blocks, the first one being for practice and therefore not included in the analysis. For simplification reasons, we have left these results out of the manuscript, reporting them here instead. The analysis indicated a significant three-way interaction between block, sex, and maltreatment (F(8,5656)=4.38, p<.001, $\eta_p{}^2$=.006) and between block, sex and psychopathology (F(8,5656)=2.93, p=.003, $\eta_p{}^2$=.004). For the former, pairwise comparisons indicated that maltreated females made more avoidance errors compared to maltreated males during blocks 3,6,7, and 8. For the latter, low psychopathology females made more avoidance errors than low psychopathology males during the same blocks (Figure A17).

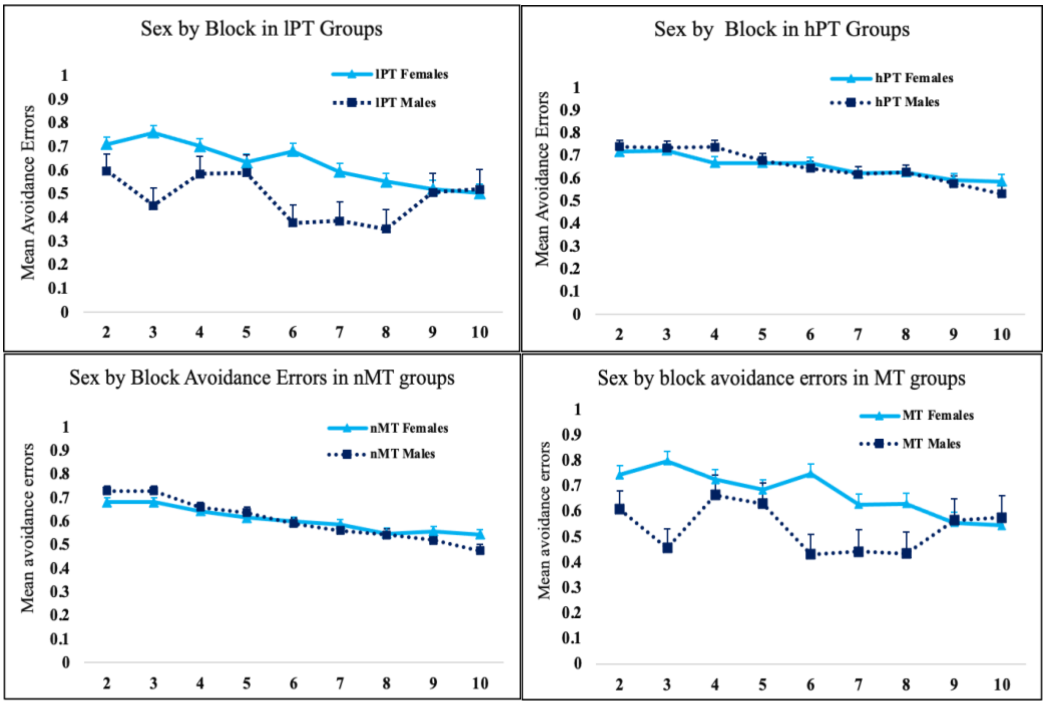


Figure A17. Interactive effects of maltreatment, psychopathology, and sex on avoidance errors.

Results by block.

A.11 Emotion responses by emotion depicted

Table A15. Confusability matrix of emotion responses by emotion depicted by groups

Emotion depicted	Emotion identified: *Anger*	*Fear*	*Disgust*	*Happiness*	*Sadness*	*Surprise*
Control						
Anger	-	3.90 (6.79)	16.23 (21.16)	0.55 (1.97)	1.42 (3.68)	7.03 (10.74)
Fear	1.26 (3.17)	-	6.32 (11.40)	0.66 (2.60)	2.64 (5.53)	16.84 (15.51)
Disgust	19.14 (26.28)	1.78 (4.52)	-	0.62 (2.46)	11.02 (12.27)	1.20 (4.59)
Happiness	0.66 (2.24)	0.80 (2.34)	0.82 (2.32)	-	0.93 (2.91)	1.73 (4.30)
Sadness	1.97 (1.97)	3.40 (6.26)	5.96 (10.72)	0.68 (2.28)	-	1.23 (3.64)
Surprise	0.84 (2.55)	7.42 (11)	1.80 (5.35)	2.57 (4.79)	0.90 (2.75)	-
PT						
Anger	-	6.71 (12.58)	15.98 (19.35)	2.44 (6.36)	2.76 (5.54)	10.20 (12.23)
Fear	2.90 (5.56)	-	11.36 (13.85)	1.83 (4.74)	3.83 (6.54)	22.67 (18.16)
Disgust	22.26 (26.84)	3.69 (8.64)	-	1.91 (4.75)	13.43 (13.91)	2.64 (5.65)
Happiness	2.15 (4.46)	1.83 (4)	2.44 (5.42)	-	2.20 (4.23)	4.01 (6.41)
Sadness	3.77 (3.77)	5.98 (9.48)	8.83 (14.03)	1.80 (5.15)	-	4.01 (8.12)
Surprise	2.15 (4.08)	10.37 (15.19)	3.54 (7)	4.30 (7.15)	2.47 (4.91)	-
Resilient						
Anger	-	4.16 (7.77)	15.66 (18.83)	1.00 (2.42)	1.83 (5.54)	4.66 (6)
Fear	2.33 (4.68)	-	18.50 (23.38)	1.33 (3.45)	1.66 (6.54)	17.83 (14.54)
Disgust	25.00 (34.34)	3.16 (7.24)	-	0.83 (2.30)	13.33 (13.91)	1.66 (4.42)
Happiness	4.83 (15.83)	1.66 (3.30)	2.33 (4.86)	-	1.33 (4.23)	1.66 (3.03)
Sadness	1.33 (1.33)	3.50 (6.96)	6.50 (7.89)	1.16 (3.13)	-	1.33 (3.45)
Surprise	0.66 (1.72)	7.33 (8.38)	4.16 (7.20)	2.66 (3.65)	1.50 (4.91)	-
MT + PT						
Anger	-	5.31 (8.1)	21.13 (23.88)	2.36 (4.87)	2.72 (5.14)	10.50 (13.07)
Fear	3.68 (6.72)	-	12.95 (15.43)	2.22 (4.95)	4.50 (6.01)	22.54 (16.41)
Disgust	23.86 (27.55)	3.54 (5.55)	-	1.40 (4.01)	12.18 (11.81)	3.18 (5.93)
Happiness	2.04 (4.13)	1.86 (4.43)	2.50 (4.77)	-	2.50 (4.82)	2.81 (5.88)
Sadness	3.81 (3.81)	6.86 (7.77)	7.68 (11.65)	2.13 (5.13)	-	2.63 (5.36)
Surprise	2.86 (6.78)	8.31 (9.41)	5.13 (8.55)	3.45 (5.93)	2.50 (4.53)	-

Notes*:* This table shows means (and standard deviations) in % of participants' response (i.e., emotion identified) for each of the six emotions depicted; **Control** = No maltreatment, no psychopathology; **PT** = High Psychopathology, no Maltreatment; **Resilient** = Maltreatment, Low Psychopathology; MT+PT = Maltreatment, High Psychopathology.

A.12 Bayes Factors (BF_{10}) for the confusability matrix data

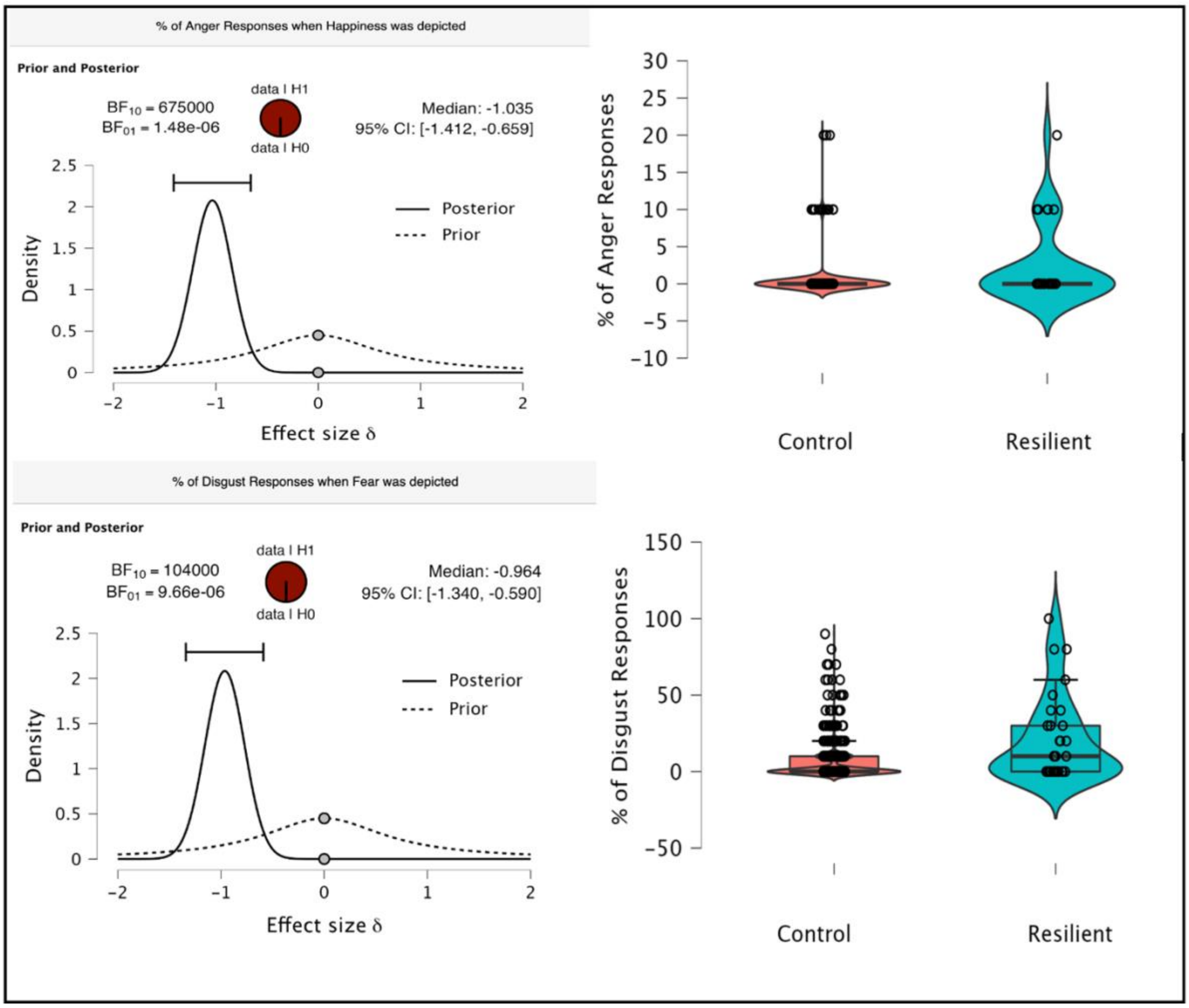
Table A16. Bayes Factors (BF10) for the confusability matrix data. Comparisons between Control vs. Resilient and PT vs. MT +PT groups

	Emotion identified					
Emotion depicted	***Anger***	***Fear***	***Disgust***	***Happiness***	***Sadness***	***Surprise***
Control vs. Resilient						
Anger	-	0.24	0.20	0.20	0.20	0.53
Fear	0.24	-	103521.47*	1.41	0.32	0.20
Disgust	0.29	0.32	-	1.55	2.27	0.24
Happiness	674986.71*	0.32	0.42	-	0.38	0.20
Sadness	0.22	0.20	0.22	0.20	-	0.20
Surprise	0.22	0.20	0.92	0.67	0.24	-
PT vs. MT +PT						
Anger	-	0.26	0.66	0.13	0.17	0.14
Fear	0.28	-	0.17	0.14	0.14	0.13
Disgust	0.15	0.13	-	0.53	0.36	0.25
Happiness	0.13	0.13	0.13	-	0.18	0.66
Sadness	0.13	0.15	0.18	0.13	-	1.18
Surprise	0.21	0.33	0.46	0.14	0.13	-

Notes: This table shows BF_{10} factors for the comparisons of emotion responses between the control and maltreated group (i.e., resilient) and between the high psychopathology versus high psychopathology and maltreatment group, for each of the six emotions depicted.

Bayes Factor Analysis showed that the resilient group was different compared to the control group for responses of anger and disgust. Specifically, resilient youth showed more response bias towards anger when happiness was depicted, and more disgust responses when fear was depicted (Figure A12).

Figure A18. Prior and posterior distributions and % of anger and disgust responses in the control and resilient groups.



Notes: The panels on the right show mean % of anger and disgust responses between the control and resilient groups. Errors bars show SEM.

A.13 Sex Differences in psychopathology subtypes following CM

The existing literature indicates that sex can "*impact both the nature and severity of psychiatric outcome following maltreatment*", and that "*maltreatment-related psychiatric disorders are associated with a greater prevalence of internalizing psychopathology in females, and greater prevalence of externalizing psychopathology in males*". At the request of one of the reviewers, we have examined this potential effect by running a sex by maltreatment post-hoc analysis to predict Internalizing and Externalizing CBCL sub-scores, respectively. For the internalizing psychopathology, the analysis revealed a main effect of maltreatment (F(1,824)=151.64, p<.001, η_p^2=.155; Figure 3A). No significant main effect of sex (F(1,824)=.004, p=.94, η_p^2=5.311e-6) or interaction between sex and maltreatment were found (F(1,824)=.011, p=.73, η_p^2=1.381e-4). For the externalising psychopathology, a similar pattern of results was observed – a main effect of maltreatment (F(1,824)=120.26, p<.001, η_p^2=.127), a non-significant main effect of sex (F(1,824)=.05, p=.82,

η_p^2=6.008e-5), and a non-significant interaction between sex and maltreatment (F(1,824)=.04, p=.83, η_p^2=5.493e-5; Figure 3B).

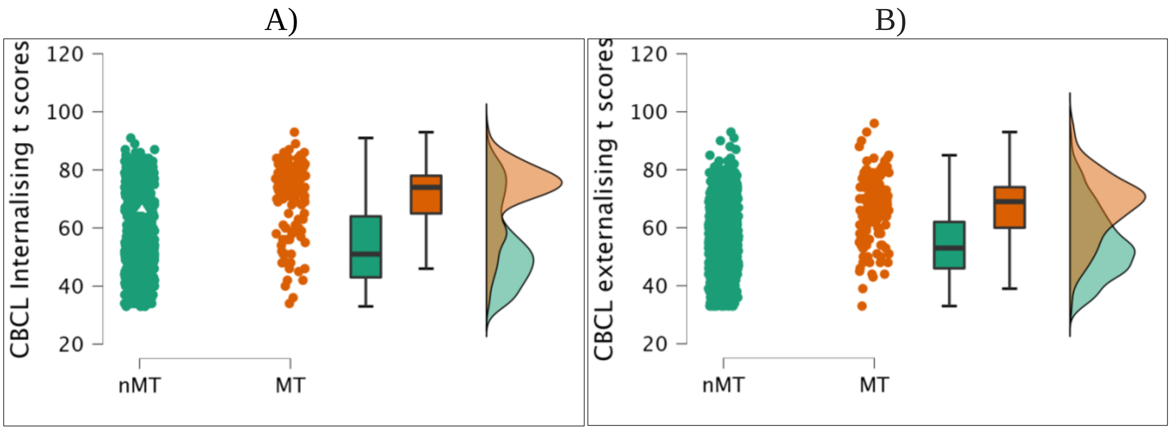


Figure A19. Maltreatment effects on internalising and externalising psychopathology

A.14 Emotion recognition analysis by internalizing and externalizing subtypes of psychopathology

Table A17. Main and interactive effects of CM and internalizing psychopathology on emotion recognition

Emotion Recognition					
Main effects	***F***	***df***	***p***	η_p^2	***Post-hoc comparisons***
Psychopathology	15.14	1, 817	*p*<.001	.018	Low > High
Sex	16.54	1,817	*p*<.001	.020	Females > Males
Covariates					
Pubertal category	33.92	1,817	*p*<.001	.040	-
SES	25.31	1,817	*p*<.001	.030	-
IQ	15.46	1,817	*p*<.001	.019	-
2-Way Interactions					
Emotion by Sex	7.59	5, 4085	*p*<.001	.009	**Disgust**: Females > Males
3-Way Interactions					
Emotion by Sex by Maltreatment	2.33	5, 4085	.039	.003	**Disgust:** Maltreatment:

					Females > Males

Notes: Covariates evaluated in the model were SES = 0.125, mean-centred IQ=1.245, and pubertal status (1 = pre/early puberty; 2 = mid/late/post puberty). The adjustment for multiple comparisons was obtained using the Bonferroni correction.

Table A18. Main and interactive effects of CM and externalizing psychopathology on emotion recognition

		Emotion Recognition			
Main effects	***F***	***df***	***p***	η_p^2	***Post-hoc comparisons***
Maltreatment	7.84	1, 817	.005	.010	nMT > MT
Sex	31.42	1, 817	*p*<.001	.037	Females > Males
Covariates					
Pubertal category	34.35	1,817	*p*<.001	.040	-
SES	34.29	1,817	*p*<.001	.040	-
IQ	22.55	1,817	*p*<.001	.027	-
2-Way Interactions					
Emotion by Sex	8.52	5, 4085	*p*<.001	.010	**Sadness, Disgust**: Females > Males
3-Way Interactions					
Emotion by Sex by Maltreatment	2.33	5, 4085	.040	.003	**Disgust**: Maltreatment: Females >Males No Maltreatment: Females >Males

Notes: Covariates evaluated in the model were SES = 0.125, mean-centred IQ=1.245, and pubertal status (1 = pre/early puberty; 2 = mid/late/post puberty). The adjustment for multiple comparisons was obtained using the Bonferroni correction.

A.15 Comorbidities

Table A19. Participants' comorbidities in the psychopathology groups

	High Psychopathology	Psychopathology + Maltreatment
Current Diagnoses (in %)	**N= 172**	**N=110**
ADHD	46.51	50.9
ODD	78.48	90
DMDD	2.32	2.72
SUD	14.53	14.54
Anxiety	13.37	18.18
OCD	2.32	3.63
TIC	1.74	0.9
PTSD	6.39	15.45
Elimination Disorders	4.65	7.27
Eating Disorders	0.57	0.9
BPD	0	0
Lifetime Diagnoses (in %)		
ADHD		
ODD	3.48	90.9
DMDD	2.32	2.72
SUD	18.60	19.09
Anxiety	20.93	21.81
OCD	2.32	3.63
TIC	3.48	3.63
PTSD	8.13	25.45
Elimination Disorders	12.2	25.45
Eating Disorders	1.16	1.81
BPD	0	0

Notes: ADHD, attention-deficit/hyperactivity disorder; ODD, oppositional defiant disorder; DMDD, disruptive mood dysregulation disorder SUD, substance use disorder; OCD, obsessive–compulsive disorder; PTSD, post-traumatic stress disorder; elimination disorders = enuresis/ encopresis; BPD, borderline personality disorder.

APPENDIX B: ANS FUNCTIONING SUPPLEMENTARY INFORMATION

B1. Distribution of participants per group, sex, and site

Table B20. Distribution of participants per group, sex, and site

Site	Total *N*	$Control_f$ *n*	$Control_m$ *n*	MT_f *n*	MT_m *n*	High P_f *n*	High P_m *n*	MT + High P_f *n*	MT + High P_m *n*
Aachen	135	35	33	3	3	20	15	12	14
Frankfurt	113	37	29	1	3	7	12	14	10
Birmingham	59	29	21	2	0	1	3	2	1
Athens	28	22	2	1	0	0	1	2	0
Bilbao	55	22	10	1	0	10	1	9	2
Southampton	26	14	8	0	0	0	4	0	0
Barcelona	23	8	0	0	0	10	2	2	1
Basel	34	25	5	2	0	1	0	1	0
Budapest	4	0	0	0	0	2	2	0	0

Amsterdam	62	34	4	2	0	8	0	13	1
	539	**226**	**112**	**12**	**6**	**59**	**40**	**55**	**29**

Notes: $_{f/m}$=female/male; Control = No Psychopathology, No Maltreatment; MT = Maltreatment only; High P = High Psychopathology only; MT+ High P= Maltreatment and High Psychopathology.

B2. RMSSD and PEP analyses

As additional exploratory analyses, we analyzed two more measures of PNS and SNS functioning respectively. For PNS, we investigated the Root Mean Square of Successive Differences between normal heartbeats (RMSSD). For SNS, the additional dependent variable was the pre-ejection period (PEP), defined as the period between the onset of the left ventricular depolarization and the opening of the aortic valve. PEP was log10 transformed to reach normalization and one outlier (i.e., value + 3 SD away from the mean) was removed from the analysis. In line with the findings reported in the manuscript, covariates were regressed from each of these two dependent variables, and standardised residuals were used when performing the analysis of variance. For RMSSD, the 2 (Maltreatment: yes/no) by 2 (Psychopathology: low/high) by 2 (Sex: females/males) analysis of variance yielded a main effect of sex (Females < Males), and two-way interactions between maltreatment and psychopathology, and sex and psychopathology. In line with our main findings, post-hoc comparisons using the Bonferroni correction showed that when psychopathology was low, maltreated youth exhibited higher RMSSD compared to the non-maltreated group. No significant differences were found between maltreated and non-maltreated groups when psychopathology was high. For the sex by psychopathology interaction, post-hoc comparisons showed that low psychopathology females exhibited lower RMSSD than low psychopathology males, but no significant differences were found when psychopathology was high. For the PEP, the 2 (Maltreatment: yes/no) by 2 (Psychopathology: low/high) by 2 (Sex: females/males) analysis showed a main effect of psychopathology, whereby youth with low psychopathology had a lower PEP compared to those with high psychopathology. A significant interaction was also found between sex and psychopathology, where high psychopathology males exhibited higher PEP than low psychopathology males (notwithstanding, the post-hoc comparisons were not significant after the Bonferroni correction).

Table B21. Main and Interactive effects of maltreatment, Psychopathology and Sex on resting RMSSD and PEP

RMSSD					
Main effects	***F***	***df***	***p***	η_p^2	***Post-hoc comparisons***
Maltreatment	0.43	1, 418	.510	.000	-
Psychopathology	3.83	1, 418	.051	.009	-
Sex	5.53	1, 418	**.019***	.013	**Females < Males**
2-Way Interactions					
Maltreatment by Psychopathology	9.14	1, 418	**.003***	.021	**Maltreated - Low psychopathology > Maltreated - High psychopathology**
Sex by Psychopathology	6.63	1,418	**.010**	.015	Low psychopathology: **Females < Males** High Psychopathology: n.s.
Sex by Maltreatment	3.68	1,418	.055	.009	-
PEP					
Main effects					
Maltreatment	1.18	1, 417	.272	.003	-
Psychopathology	4.11	1,417	**.043***	.010	**Low < High**
Sex	1.67	1,417	.196	.004	-
2-Way Interactions					
Sex by Maltreatment	2.88	1,417	.090	.008	-
Sex by Psychopathology	4.16	1,417	**.042***	.010	n.s.

Notes: RMSSD = Root Mean Square of Successive Differences between normal heartbeats; PEP = Pre-ejection period; BMI = Body Mass Index; SES=Socioeconomic Status; The adjustment for multiple comparisons were obtained using the Bonferroni correction.

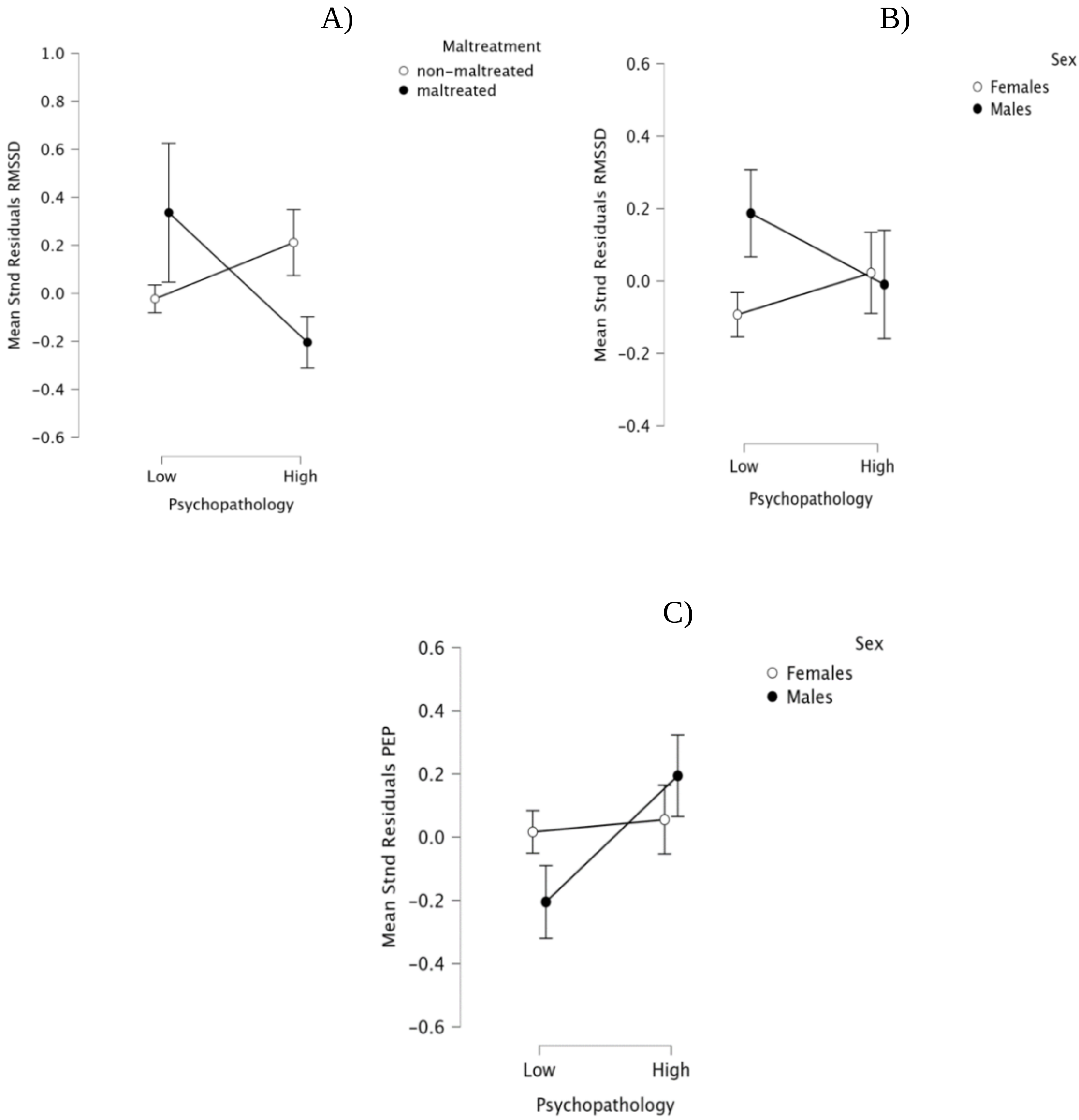


Figure B20. Maltreatment by psychopathology and sex by psychopathology interactions on RMSSD.

B3. Internalizing and externalizing psychopathology effects on resting HRV and EDA during the Countdown task

Given that our design did not distinguish between internalizing and externalizing psychopathology, we further examined specific associations between maltreatment and these psychopathology subtypes. For HRV, the 2 (Maltreatment: yes/no) by 2 (*Internalizing* Psychopathology: low/high) by 2 (Sex: females/males) analysis of variance showed a significant interaction between maltreatment and *Internalizing* Psychopathology. While post-hoc comparisons were non-significant due to loss of statistical power, data visualization of this interaction showed the same pattern of results reported in our main analysis. Specifically, maltreated youth exhibited higher HRV than their non-maltreated counterparts when *Internalizing* psychopathology was low, but no differences were found when *Internalizing* Psychopathology was high. For

EDA during anticipation of the aversive stimulus, this analysis showed higher EDA in the maltreated groups compared to the non-maltreated group; however, this difference was not statistically significant. For EDA during response, a significant main effect of maltreatment was reported (Maltreated > non-Maltreated) (Table 4).

Similarly, for HRV, the 2 (Maltreatment: yes/no) by 2 (*Externalizing* Psychopathology: low/high) by 2 (Sex: females/males) analysis yielded a significant interaction between maltreatment and *Externalizing* psychopathology. As reported above, while post-hoc comparisons were non-significant, visualisation of this interaction showed that maltreated youth had higher HRV than the non-maltreated group in the presence of low *Externalizing* psychopathology, but not when *Externalizing* psychopathology was high. Finally, for EDA, no significant main or interactive effects were found during either the anticipation or the response phase of the countdown task.

Table B22. Main and Interactive Effects of Maltreatment, Internalizing Psychopathology and Sex on resting HRV and EDA during the Countdown Task

			Resting HRV		
Main effects	***F***	***df***	***p***	η_p^2	***Post-hoc comparisons***
Maltreatment	1.15	1, 417	.283	.003	-
Internalizing Psychopathology	2.65	1, 417	.104	.006	-
Sex	0.03	1, 417	.865	6.938e-5	-
2-Way Interactions					
Maltreatment by *Internalizing Psychopathology*	5.75	1, 417	**.017***	.014	**n.s.**
			EDA - Countdown Task – Anticipation		
Main effects					
Maltreatment	3.81	1, 489	.052	.008	-
Internalizing Psychopathology	2.06	1,489	.152	.004	-
Sex	1.23	1,489	.266	.003	-
2-Way Interactions					

Maltreatment by Sex	3.21	1,489	.073	.007	-
			EDA – Countdown Task – Response		
Main effects					
Maltreatment	5.31	1,487	**.022***	.011	**Maltreated > non-Maltreated**
Internalizing Psychopathology	1.81	1,487	.179	.004	-
Sex	2.93	1,487	.087	.006	-

Notes: HRV = Heart Rate Variability; EDA = Electrodermal Activity; The adjustment for multiple comparisons were obtained using the Bonferroni correction.

Table B23. Main and Interactive Effects of Maltreatment, Externalizing Psychopathology and Sex on resting HRV and EDA during the Countdown Task

			HRV - rest		
Main effects	***F***	***df***	***p***	η_p^2	***Post-hoc comparisons***
Maltreatment	0.51	1, 417	.476	.001	-
Externalizing Psychopathology	2.35	1, 417	.126	.006	-
Sex	0.16	1, 417	.684	3964e-4	-
2-Way Interactions					
Maltreatment by *Externalizing Psychopathology*	4.97	1, 417	**.026***	.012	**n.s.**
			EDA - Countdown Task – Anticipation		
Main effects					
Maltreatment	2.10	1, 489	.148	.004	-
Externalizing Psychopathology	0.09	1,489	.759	1.925e-4	-
Sex	0.59	1,489	.440	.001	-
2-Way Interactions					
Maltreatment by Sex	3.67	1,489	.056	.007	-
			EDA – Countdown Task – Response		
Main effects					
Maltreatment	2.74	1,487	.098	.006	-

Externalizing Psychopathology	0.03	1,487	.857	6.630e-5	-
Sex	2.08	1,487	.150	.004	-

Notes: HRV = Heart Rate Variability; EDA = Electrodermal Activity; The adjustment for multiple comparisons were obtained using the Bonferroni correction.

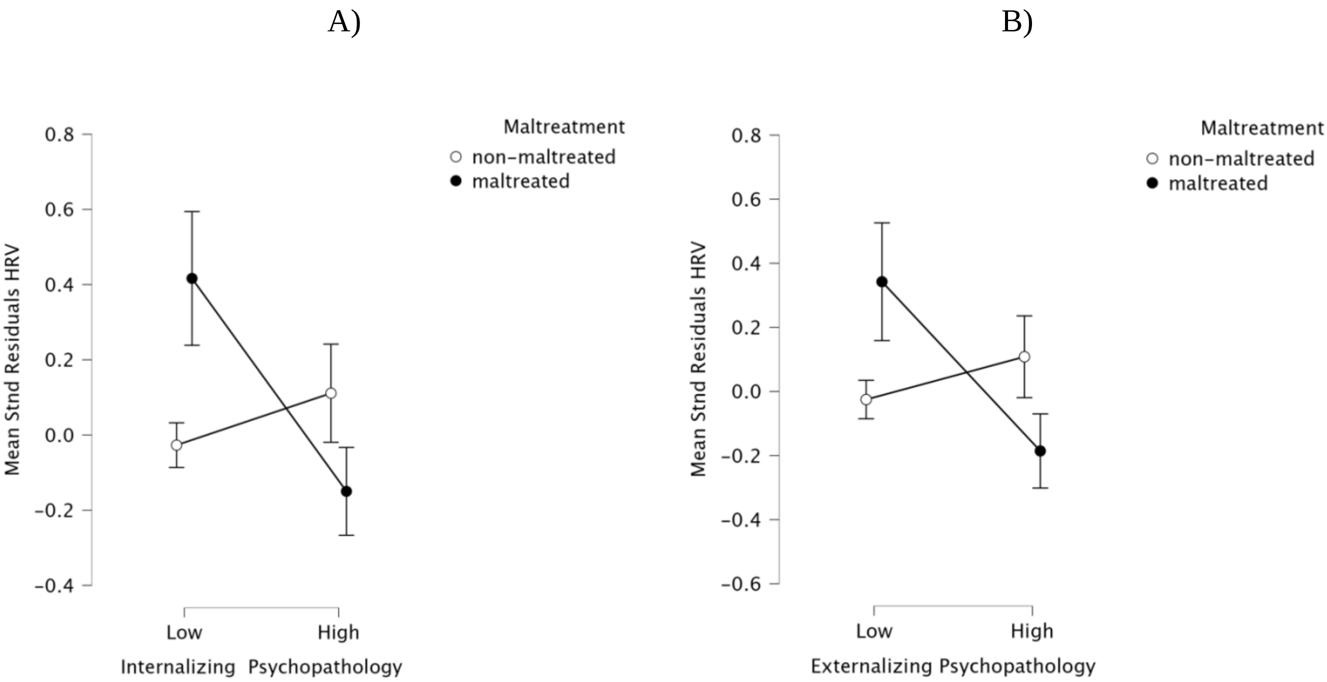


Figure B21. Maltreatment by internalizing and externalizing psychopathology interactions on resting HRV

B4. EDA results based on presence/absence of anxiety disorders.

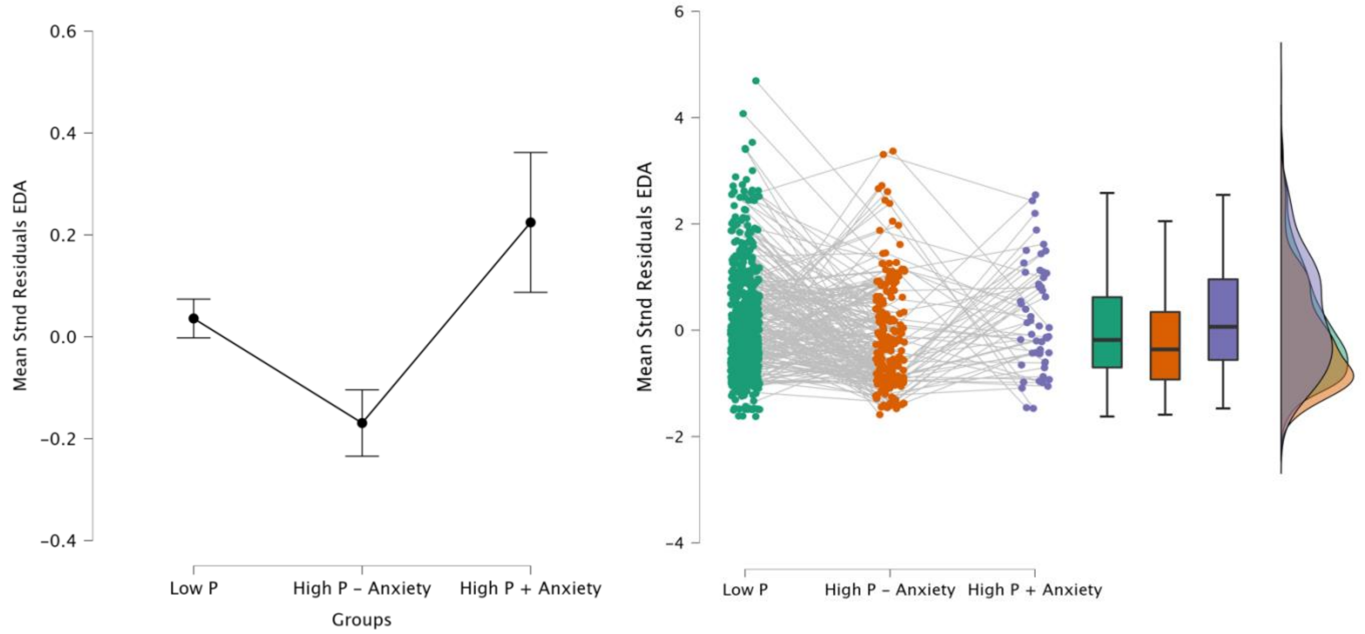
To further explore psychopathology effects on EDA, we divided high psychopathology participants into groups based on presence/absence of anxiety disorders (high P – Anxiety; high P + Anxiety). This is due to previous literature reporting that anxious participants exhibit increased EDA during stress, as opposed to reduced EDA in other disorders (e.g., depression, CD). We therefore tested the hypothesis that the lack of psychopathology effect on EDA reported in the main manuscript might be due to different psychopathology effects cancelling each other out. During the anticipation phase, this analysis showed that participants with high psychopathology and anxiety disorders (i.e., GAD, OCD or PTSD) exhibited higher EDA compared to those with high psychopathology without anxiety disorders; however, these differences were not significant after the *p* value correction. During the response phase, a significant main effect of psychopathology/anxiety was found - post-hoc comparisons using the Bonferroni correction showed that participants with low psychopathology exhibited higher EDA compared to those with high psychopathology and no anxiety disorders (High P – Anxiety). Moreover, youth with high psychopathology and anxiety disorders (High P +Anxiety) exhibited higher EDA compared to the high P – Anxiety group. While beyond the scope of our study, these findings replicate previous literature reporting higher EDA associated with Anxiety, as opposed to other psychopathological symptoms such as depression or conduct problems.

Table B24. Main and Interactive Effects of Maltreatment, Psychopathology (With and Without Anxiety) and Sex on EDA during the Countdown Task

			EDA – Anticipation		
Main effects	***F***	***df***	***p***	η_p^2	***Post-hoc comparisons***
Maltreatment	0.75	1, 470	.387	.002	-
Psychopathology/ Anxiety	3.51	1,470	**.031***	.015	**n.s.**
Sex	1.45	1,470	.228	.003	-
2-Way Interactions					
Maltreatment by *Psychopathology/ Anxiety*	0.71	1,470	.489	.003	-
Maltreatment by Sex	1.14	1,470	.286	.002	-
Psychopathology/ Anxiety by Sex	0.30	1,470	.741	.001	-
			EDA – Response		
Main effects					
Maltreatment	7.63	1,468	**.006***	.016	**Maltreated > non-Maltreated**
Psychopathology /Anxiety	6.40	1,468	**.002***	.027	**Low P > High P–Anxiety. High P + Anxiety > High P-Anxiety**
Sex	1.86	1,468	.172	.004	-
2-Way Interactions					
Maltreatment by *Psychopathology/ Anxiety*	0.59	1,468	.550	.003	-
Maltreatment by Sex	0.20	1,468	.654	4.288e-4	-
Psychopathology/ Anxiety by Sex	1.80	1,468	.166	.008	-

Notes: EDA = Electrodermal Activity; The adjustment for multiple comparisons were obtained using the Bonferroni correction.

Anticipation



Response

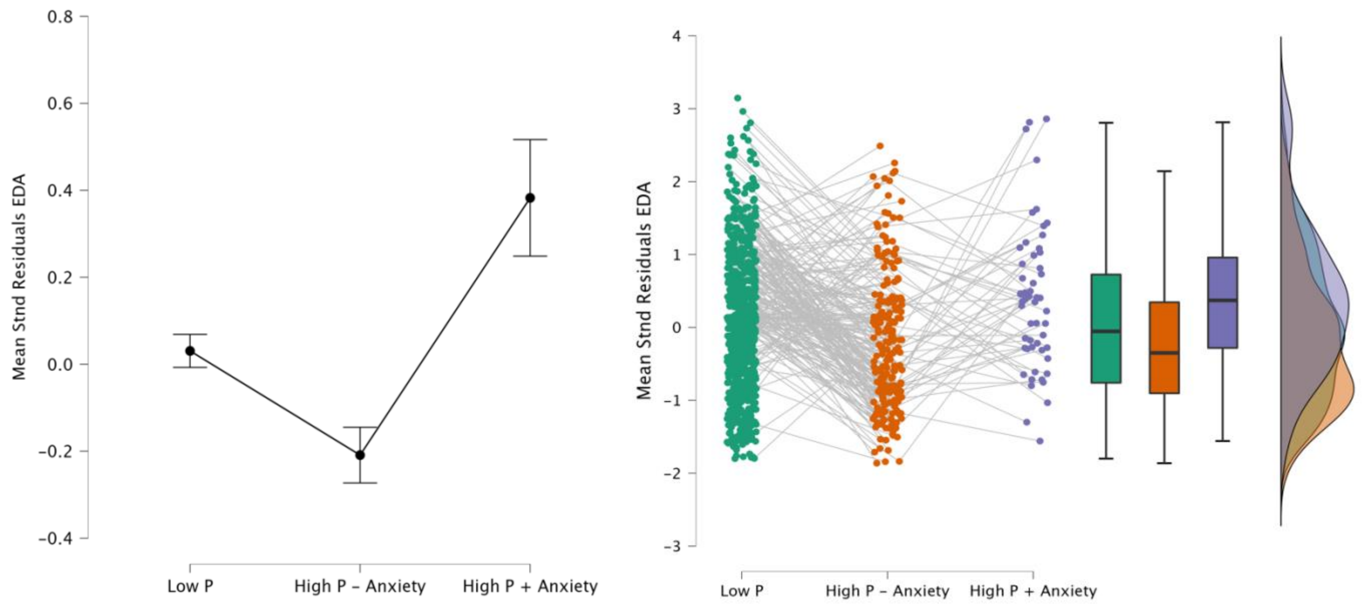


Figure B22. Mean Standardised Residuals for EDA in the three groups. – Low P (Low Psychopathology), High P – Anxiety(High Psychopathology without Anxiety) and High P + Anxiety (High Psychopathology with Anxiety).

B5. Participants' Comorbidities

Table B25. Participants' current and lifetime comorbid diagnoses in the psychopathology groups

	High Psychopathology	**Psychopathology + Maltreatment**	**Group effects**
Current Diagnoses (in %)	N= 99	N=84	x^2
CD	100	100	0
ADHD	51.80	52.77	0.01
ODD	85.55	87.5	0.72
DMDD	4.81	4.16	0.84
SUD	13.25	25	3.49
Anxiety	15.66	19.44	0.38
OCD	2.41	1.38	0.21
TIC	0	0	0
PTSD	8.43	12.5	0.68
Elimination Disorders	7.22	5.55	0.17
Eating Disorders	1.2	1.38	0.01
BPD	1.2	1.38	0.01
Lifetime Diagnoses (in %)			
ADHD	51.8	52.77	0.01
ODD	90.36	91.66	0.08
DMDD	4.81	4.16	0.03
SUD	18.07	34.72	5.58**
Anxiety	25.3	23.61	0.06
OCD	2.41	1.38	0.21
TIC	2.41	2.77	0.02
PTSD	10.83	22.22	3.69
Elimination Disorders	14.45	22.22	1.57
Eating Disorders	1.2	1.38	0.01
BPD	1.2	1.38	0.01

Notes: ADHD, attention-deficit/hyperactivity disorder; ODD, oppositional defiant disorder; DMDD, disruptive mood dysregulation disorder SUD, substance use disorder; OCD, obsessive–compulsive disorder; PTSD, post-traumatic stress disorder; elimination disorders = enuresis/ encopresis; BPD, borderline personality disorder.

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