The impact of trauma: a focus on the neural correlates of intergenerational transmission of child maltreatment

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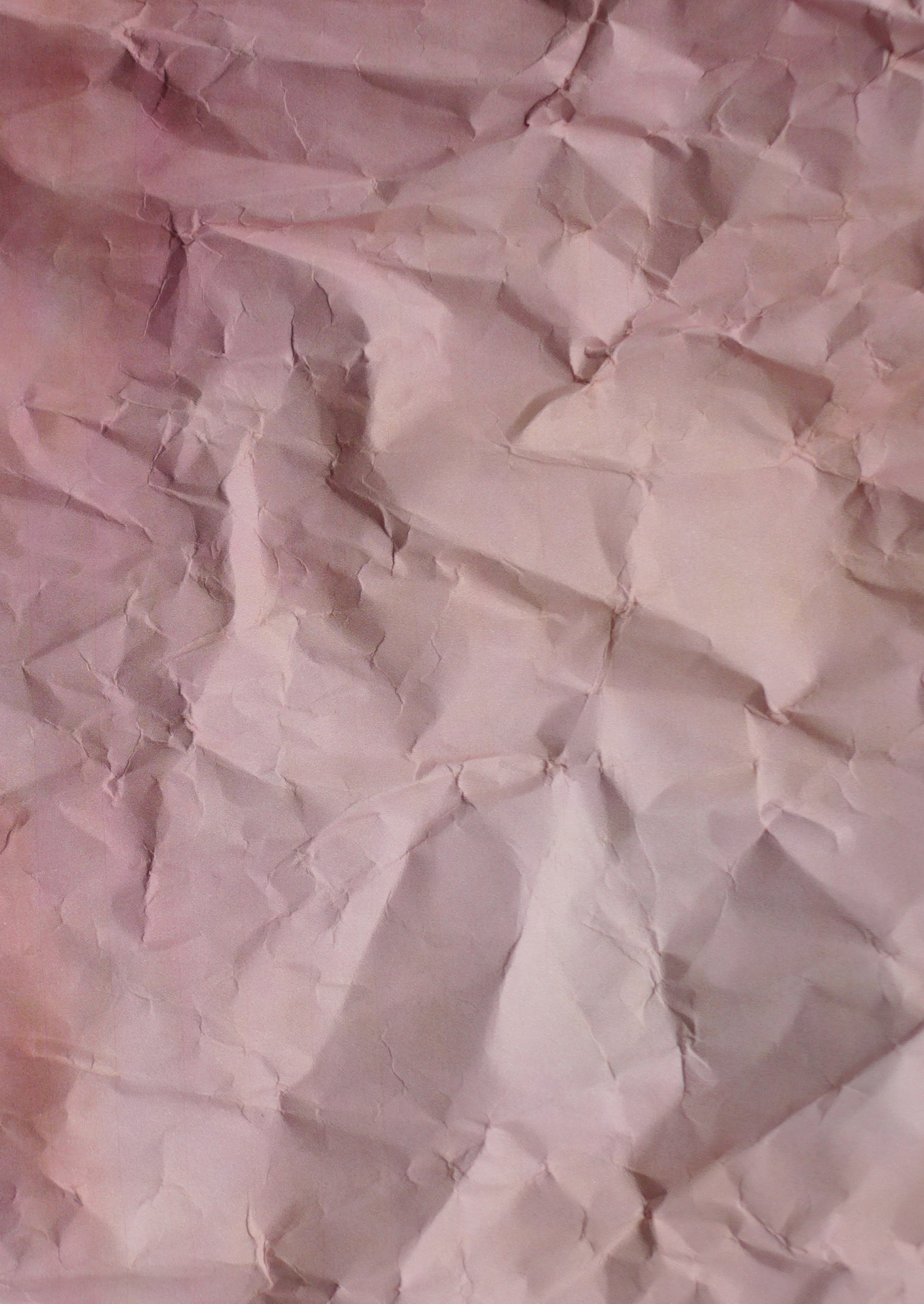

Chapter 1

Introduction

The majority of all individuals will experience a potentially traumatic event at some point during their life, with lifetime estimates ranging from 60-90% (Kessler et al., 2017; Kilpatrick et al., 2013; Thordardottir et al., 2015). People have a natural adaptive ability to cope with stress and trauma. Nevertheless, some type of events, for example childhood abuse or neglect, are so stressful, that coping strategies may be inadequate, leading to excessive or prolonged stress responses (Chrousos, 2009; Dhabhar, McEwen, & Spencer, 1997). In those instances, the impact on our emotional, psychological and physical wellbeing can be devastating. The experience of severe or chronic stress due to traumatic events is associated with the development and maintenance of numerous physical and mental illnesses such as cardiovascular diseases, anxiety disorders, posttraumatic stress disorder (PTSD), and depression (e.g., Bryant, Creamer, O'Donnell, Silove, & McFarlane, 2011; Frodl & O'Keane, 2013; Heim & Nemeroff, 2001; Kilpatrick et al., 2003; Lupien, McEwen, Gunnar, & Heim, 2009; Seo, Tsou, Ansell, Potenza, & Sinha, 2013), which forms a major cause of numerous disabilities across the lifespan (Van der Werff, Van den Berg, Pannekoek, Elzinga, & Van der Wee, 2013). Because of its high prevalence and damaging effects on our wellbeing, stress has been labeled as the "Health Epidemic of the 21st Century" (WHO, 2013).

Some stressful events are potentially traumatic. The DSM-5 definition of a traumatic (A1) event entails "actual or threatened death, serious injury, or sexual violence" (American Psychiatric Association, 2013). There has, however, been an ongoing debate about this A1 criterion of PTSD, because research shows that other stressful (non-A1) events (such as childhood neglect) are associated with similar or even higher rates of PTSD symptoms than A1 events (such as childhood abuse; e.g., Anders, Frazier, & Frankfurt, 2011; Cameron, Palm, & Follette, 2010; Gold, Marx, Soler-Baillo, & Sloan, 2005; Long et al., 2008; Mol et al., 2005; Roberts et al., 2012; Robinson & Larson, 2010). This emphasizes the need to further investigate the impact of different types of stressful and traumatic events (see Chapter 2 of this dissertation).

While stress affects people of all ages, research shows that the experience of stressful life events during childhood is more strongly associated with the development of psychopathology than negative life events experienced later in life (e.g., Spinhoven et al., 2010). Worldwide, over 50% of all children are exposed to (potentially traumatic) stress (Fenoglio, Brunson, & Baram, 2006). One of the explanations for the particularly high impact of stressful life events during childhood is the fact that it often takes place within the family context. One of the most replicated findings in the field of clinical psychology and psychiatry is the enduring association between exposure to stressful family environments during childhood and the development of any form of psychopathology (Conway, Raposa, Hammen, & Brennan, 2018; Green et al., 2010). Children are still relatively helpless and dependent on their caregivers and growing up in adverse family circumstances may turn parents into a source of both safety and threat. This endangers the healthy development of children, since perceived safety of attachment figures is vital for this development.

Children have also encountered fewer other (more positive) experiences than older individuals and their coping resources are not yet optimally developed.

The experience of stressful and potentially traumatic events during childhood has been consistently associated with an increased risk of long-lasting behavioral, physical and mental health problems (e.g., Heim, Shugart, Craighead, & Nemeroff, 2010; McCrory, De Brito, & Viding, 2011; Norman et al., 2012; Spinhoven, Penninx, Van Hemert, De Rooij, & Elzinga 2014; Twardosz & Lutzker, 2010) and poor outcomes regarding social and academic functioning, and economic productivity (e.g., Currie & Spatz Widom, 2010; Lansford et al., 2002; Shirtcliff et al., 2009). Moreover, it has been associated with remarkable structural and functional alterations in the brain, even decades later (e.g., Dannlowski et al., 2012, Teicher et al., 2003). The brain is particularly sensitive to stress during early childhood, probably because of the important neural changes during this period (Lupien et al., 2009). Neural alterations following negative life events during childhood are associated with the development of difficulties on a behavioral, emotional and psychological level and are therefore designated as an explanatory mechanism for the impact of stressful and traumatic events (e.g., Dannlowski et al., 2012; Heim & Nemeroff, 2001; Lupien et al., 2009). Hence, in Chapter 3, 4 and 5 of this dissertation we zoom in on the neurobiological consequences of trauma.

One of the most common types of stressful and potentially traumatic events during childhood are various forms of child maltreatment (Martins, De Carvalho Tofoli, Von Werne Baes, & Juruena, 2011), including a spectrum of physical, emotional and sexual forms of abuse, as well as physical and emotional neglect (e.g., Krug, Dahlberg, Mercy, Zwi, & Lozano, 2002). Child maltreatment can be defined as any act of commission (abuse) or omission (neglect) by a parent or other caregiver that results in potential or actual harm, or threat of harm to the child's health, survival, development or dignity in the context of a relationship of responsibility, trust or power (WHO, 1999). It is a widespread problem affecting millions of children around the globe (Savage, Tarabulsy, Pearson, Collin-Vézina, & Gagné, 2019; Stoltenborgh, Bakermans-Kranenburg, Alink, & Van IJzendoorn, 2015). In the Netherlands, 89.160 to 127.190 children (2.6%-3.7% of all 0-17-year-old children) experienced at least one form of child maltreatment in 2017 (Van Berkel, Prevoo, Linting, Pannebakker, & Alink, 2020). Emotional and physical neglect were the most prevalent types of maltreatment and 29% of affected children experienced more than one type of maltreatment. Moreover, the majority of these children was victimized by one or both of their parents. Most of the children (87%) were maltreated by their biological mother, 63% by their biological father and in the majority of cases (53%) both parents were involved as perpetrator (Van Berkel et al., 2020).

Exposure to childhood abuse and neglect is associated with a cascade of negative consequences that impairs psychological, social and biological development, which can persist throughout the life span (e.g., McCrory et al., 2011; Norman et al., 2012). The

devastating consequences of experienced child maltreatment are not only evident in the lives of victimized individuals, but the effects are also a burden for our society as a whole because of its long-lasting effects on mental health, obesity, child mortality, criminal behavior, risky sexual behavior and drugs and alcohol misuse (Gilbert et al., 2012). This highlights the urgent need to further increase our knowledge regarding the impact of child maltreatment on different levels in order to identify possible targets to design preventive interventions in the future. In Chapter 3, 4 and 5 of this dissertation we focus on examining the neural correlates of one of the most striking consequences of experienced childhood maltreatment, namely the increased risk of maltreating own offspring (Dubowitz et al., 2001; Madigan et al., 2019; Pears & Capaldi, 2001; Savage et al., 2019).

In sum, the aim of the current dissertation is to examine the impact of different types of stressful and traumatic events (Chapter 2), including a focus on the impact of different forms of child maltreatment on a psychological, neurological and behavioral level (Chapter 3, 4 and 5). The role of brain structure (Chapter 3) and function (Chapter 4 and 5) in intergenerational transmission of child abuse versus neglect will be investigated using a family study design. The theoretical background to the specific studies of this dissertation will be further described in the following section.

TRAUMATIC EVENTS VERSUS STRESSFUL EVENTS

While the role of childhood trauma in the aetiology and maintenance of affective disorders has been repeatedly demonstrated (e.g., Kessler, Davis, & Kendler, 1997; Shonkoff & Garner, 2012), the risk of developing psychopathology varies according to the type of traumatic event that is experienced (Briggs-Gowan et al., 2010; Kessler et al., 2017; Ozer, Best, Lipsey, & Weiss, 2003). PTSD is one of only a few disorders in the DSM (American Psychiatric Association, 2013) that requires an aetiological factor for its diagnosis, namely a traumatic event. In the DSM-IV-TR this so-called A1 criterion involves: *'experiencing, witnessing or being confronted with an event or events that involve actual or threatened death or serious injury, or a threat to the physical integrity of self or others'* (American Psychiatric Association, 2000). During the last decades there has been an ongoing debate about the validity and clinical usefulness of the A1 criterion. In the DSM-5 this A1 criterion has been narrowed to *'exposure to actual or threatened death, serious injury or sexual violence'* (American Psychiatric Association, 2013). This means that events such as the unexpected death of a family member or a close friend due to natural causes do not meet the A1 criterion of PTSD anymore. Hence, several dimensions of childhood stress or trauma, such as childhood neglect, moving or bullying, are not included in this A1 criterion, despite of the major problems they can cause later in life. This is remarkable since several studies have reported that stressful non-A1 events are associated with similar or even higher

rates of PTSD symptoms than formal A1 events (e.g., Anders et al., 2011; Cameron et al., 2010; Gold et al., 2005; Long et al., 2008; Mol et al., 2005; Roberts et al., 2012; Robinson & Larson, 2010), questioning the constricted definition of traumatic A1 events. This calls for a renewed discussion on the role and definition of stressful life events in the development of PTSD.

In Chapter 2 of this dissertation we therefore investigate whether formal DSM-IV-TR traumatic (A1) and stressful (non-A1) events differ with regard to PTSD symptom profiles using a large, mostly clinical sample. Data for this study were drawn from the Netherlands Study of Depression and Anxiety (NESDA), a longitudinal cohort study among 2,981 participants at baseline. In order to assess exposure to A1 or non-A1 events, the Life Events Checklist (LEC; Weathers, Keane, & Davidson, 2001) and the PTSD Symptom Scale - Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993) were administrated.

INTERGENERATIONAL TRANSMISSION OF CHILD MALTREATMENT

In the remaining chapters of this dissertation (Chapters 3, 4 and 5) we focus on one of the most common types of childhood trauma, namely different forms of child maltreatment, both childhood abuse and childhood neglect (Martins et al., 2011). Some of the adverse consequences of child maltreatment, such as emotion regulation difficulties, have been shown to also compromise interpersonal functioning including one's own later parenting behavior (Norman et al., 2012; Pears & Capaldi, 2001; Savage et al., 2019). Parents who have been maltreated during their childhood may have fewer resources to manage the challenges of day-to-day parenting. Maltreated parents report higher stress levels and lower emotional control capabilities. These factors are associated with a higher likelihood to show insensitive and more problematic parenting behaviors (e.g., Van Wert, Anreiter, Fallon, & Sokolowski, 2019), including maltreating behavior towards own children (Dubowitz et al., 2001; Madigan et al., 2019; Pears & Capaldi, 2001; Savage et al., 2019). Around 30% of maltreated individuals maltreat their own children, a percentage that is significantly lower in non-maltreated individuals (e.g., Berlin, Appleyard, & Dodge, 2011; Dixon, Hamilton-Giachritsis, & Browne, 2005). It is even suggested that parents who were maltreated during childhood are twice as likely to maltreat their own children (Madigan et al., 2019).

Although results of previous empirical studies on intergenerational transmission of child maltreatment (ITCM) are inconsistent and sometimes even contradictory (e.g., Renner & Shook Slack, 2006; Sidebotham & Heron, 2006), a recent umbrella synthesis of meta-analyses confirms the cycle of maltreatment hypothesis and reports a rather large umbrella effect size of nearly half a standard deviation (d = .47; Van IJzendoorn, Bakermans-Kranenburg, Coughlan, & Reijman, 2020). Several methodological challenges

contribute to previous conflicting findings, including variations in definitions of maltreatment, research designs (e.g., prospective versus retrospective, duration of longitudinal follow-up), population, sampling strategy (e.g., at risk versus representative sample), source of maltreatment reports (e.g., official records versus child or parent report and single versus multi-informant approaches) and types of maltreatment being examined (i.e., abuse versus neglect; Bartlett, Kotake, Fauth, & Easterbrooks, 2017; Buisman et al., 2020).

Unravelling the moderating and mediating mechanisms behind this ITCM is crucial to inform and shape the development of future intervention and prevention strategies to break the cycle of maltreatment. However, to date few of those mechanisms have been adequately tested and/or confirmed (Alink, Cyr, & Madigan, 2019). Most studies are focusing on the first part of the cycle and only investigate consequences of child maltreatment. Much less is known about the second part of the cycle, namely about potential risk factors for parental child maltreatment. Furthermore, when this second part of the cycle of maltreatment is examined the first part is usually not taken into account. Hence, studies directly testing mediating mechanisms that might explain ITCM are scarce (Alink et al., 2019, but see e.g., Buisman et al., 2020). To address these considerable gaps in the literature, the 3-Generation (3G) Parenting Study was designed, which will be described below and in Chapters 3, 4 and 5 of this dissertation.

THE 3-GENERATION PARENTING STUDY

Chapters 3, 4 and 5 of the current dissertation are based on an empirical three-generational extended family study on intergenerational transmission of parenting styles, stress and emotion regulation (see also Buisman et al., 2020; Compier-de Block, 2017). This 3G Parenting Study was developed to examine possible mechanisms of ITCM on multiple levels, including genetic, physiological, neural, cognitive and behavioral levels. In order to increase power to detect ITCM, we oversampled participants with an increased risk of maltreatment by recruiting target participants via three other studies that included the assessment of caregiving experiences: The Netherlands Study of Depression and Anxiety (NESDA; Penninx et al., 2008), the Longitudinal Internet Studies for the Social Sciences (LISS panel; Scherpenzeel, 2011) and a study on parenting (Joosen, Mesman, Bakermans-Kranenburg, & Van IJzendoorn, 2013). From two of those studies, individuals were invited to participate in the 3G Parenting Study when they had reported a history of experienced child maltreatment. From the third study, all participants (a high-risk group for maltreatment) were invited. Participants who agreed to participate in the 3G Parenting Study were asked permission to invite their family members (parents, partners, offspring, adult siblings, nephews, nieces and in-laws) for participation as well. We aimed to include a

family tree of participants from three (or more) generations (F1, F2 and F3) around one target participant (see Figure 1). Children had to be at least 7.5 years of age to be included, because this is the minimum age to participate in fMRI research. Families were included if at least two first-degree relatives from two generations were willing to participate.

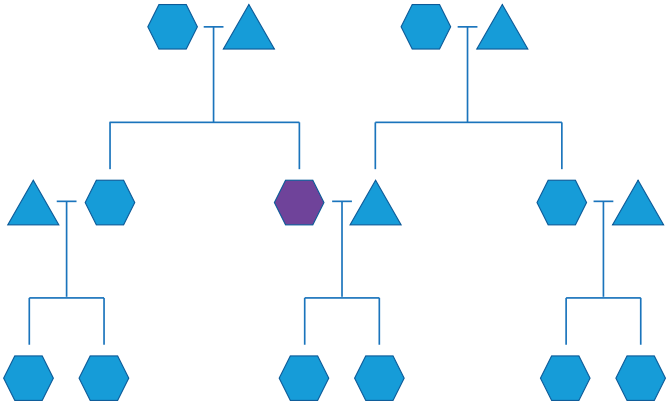

Figure 1. An example of a family tree of participants invited around the target participant (in purple).

One or two visits to our research lab were scheduled, depending on family composition. Adult participants visited the lab once with their nuclear family and once with their family of origin. Before the first lab visit, participants were asked to fill out a number of questionnaires at home. During the lab visits, participants completed several questionnaires and computer tasks and participated in different interaction tasks together with their family members. Saliva, hair, and buccal samples were collected to measure hormone levels and DNA and during some tasks heart rate and skin conductance were measured. Data collection was performed between March 2013 and May 2016. By investing a lot of time in informing and recruiting target participants and their family members and getting them enthusiastic about our study, we managed to include participants from 63 different families in our sample. The final sample of the 3G Parenting Study consisted of 395 individuals from up to four generations (with an average of 6.27 family members per family) with an age range from 7.5-88 years old. We have indeed found indications for ITCM in our sample, which demonstrates that our study design is suitable to examine possible mediators of ITCM.

NEURAL CORRELATES OF ITCM

The 3G Parenting Study was developed to assess mechanisms of ITCM on multiple levels. In the current dissertation we zoom in on investigating the neural correlates of ITCM. The

human brain plays an essential role in stress reactivity (e.g., McEwen & Gianaros, 2010). A distributed neural circuitry regulates what is perceived as threatening, and therefore stressful, and controls how to react to stress. Studies in both animals and humans have demonstrated that the brain (and its regulation of threat and stress) is particularly sensitive to stress during (early) childhood (Lupien et al., 2009). Stress at an early age can have a large impact on the neural stress-system. More specifically, experienced childhood abuse and neglect can affect brain structure, morphology and function in key regions of the limbic system including the amygdala and hippocampus (e.g., Baker et al., 2013; Teicher et al., 2003). Neural alterations in these systems following experienced child maltreatment are likely to be neural correlates of impairments in social functioning via their impact on threat and emotion processing and responding (Bremner, 1999; Elzinga & Bremner, 2002; Hart & Rubia, 2012) and the (impaired) control of aggression (Davidson, Putnam, & Larson, 2000). In this dissertation we focus on the neural correlates of two important processes in the context of child maltreatment, namely emotional face processing and social exclusion. Disruptions in these neural pathways in parents who experienced child maltreatment might make maltreated parents more vulnerable to maltreat their own children and might therefore be one of the mechanisms involved in ITCM.

While we know that neural alterations following child maltreatment include brain regions that are also involved in caregiving behavior (including the amygdala, hippocampus, insula and the inferior frontal gyrus (IFG); DeGregorio, 2013; Rilling & Mascaro, 2017; Swain & Ho, 2017), research on the neural correlates of parenting behavior in general - and maltreating parenting behavior in particular - is scarce (Pozzi et al., 2020; Van IJzendoorn et al., 2020). To date little is known about the role of neural networks involved in threat processing and stress regulation - processes relevant for parenting - in ITCM. To address this significant gap in the literature, the main focus of this dissertation is the examination of the structural and functional neural correlates of ITCM in the 3G Parenting study.

If eligible, participants (parents and their children) of the 3G Parenting study were invited for a functional magnetic resonance imaging (fMRI) session. During this session, structural MRI scans of the brain were made as well as functional MRI scans while participants were performing three tasks, including an emotional faces task and the Cyberball task. The current dissertation includes three papers (Chapter 3, 4 and 5) in which the role of neural correlates of ITCM is examined by using data from the 3G Parenting study. The association of structural and functional neural alterations with both experienced and perpetrated child abuse and neglect is examined, with which the possible mediating role of these alterations in ITCM could be studied. With regard to brain structure, we focused on the role of hippocampal volume in ITCM (Chapter 3). Regarding brain function, we first examined the role of neural emotional face processing in the amygdala, hippocampus, IFG and insula in ITCM (Chapter 4). In Chapter 5 we studied the role of neural responses to social rejection in the insula, anterior cingulate cortex (ACC) and medial prefrontal

cortex (mPFC) in ITCM. The examination of the role of hippocampal volume in ITCM will be discussed first.

ITCM and hippocampal volume

The hippocampus, a key brain structure of the limbic system, is known as one of the most plastic and stress sensitive structures of the human brain (e.g., Teicher et al., 2018). It plays an essential role in the neural circuitry regulating stress reactivity (McEwen & Gianaros, 2010). Various psychiatric disorders are associated with alterations in hippocampal volume (Geuze, Vermetten, & Bremner, 2005). Moreover, experienced childhood maltreatment has been associated with reduced hippocampal volume (e.g., McCrory et al., 2011; Riem, Alink, Out, Van IJzendoorn, & Bakermans-Kranenburg, 2015; Teicher et al., 2018; Whittle et al., 2016) in maltreated individuals with (Thomaes et al., 2010) and without psychopathology (Dannlowski et al., 2012; Teicher, Andersen, & Polcari, 2012). Furthermore, brain areas involved in context and memory processing and neural arousal and salience detection, including the hippocampus, seem to be important for parenting behavior. Indeed, MRI studies have demonstrated the involvement of the hippocampus in normative parenting behavior (Swain, Lorberbaum, Kose, & Strathearn, 2007).

Taken together, we hypothesized that hippocampal volume reduction following experienced child maltreatment might play a role in subsequent parental maltreating behavior, and hence in ITCM. However, to date little is known about the association between maltreating parenting behavior and hippocampal volume. In Chapter 3 of this dissertation we therefore describe the examination of associations of bilateral hippocampal volume with both experienced childhood maltreatment and maltreating parenting behavior, enabling the investigation of the potential role of hippocampal volume in intergenerational transmission of childhood abuse and neglect. Our study design also enables us to take heritability effects on hippocampal volume into account while examining the impact of timing of the effects.

ITCM and the neural correlates of threat processing

While alterations in brain structure might play a role in ITCM, it also seems imperative to focus on the functioning of the brain. One suggested mechanism that might play a role in ITCM is related to threat processing and its neural correlates. Experienced child maltreatment is repeatedly associated with increased threat perception and difficulties regarding emotion regulation (e.g., Briere, 2002; Pozzi et al., 2020). From an evolutionary perspective, adequately processing and responding to facial emotional expressions is important when growing up in a maltreating environment, because they can provide signs of threat or safety. However, over time, a heightened reactivity to negative emotional faces puts maltreated individuals at increased risk to develop a persistent vigilance for threat-related facial cues and an attentional bias towards negative information in general, which is

often associated with developing psychopathology (e.g., Gibb, Schofield, & Coles, 2009). Deviances in emotional face processing might also be related to parenting behavior, since facial cues of children are crucial to provoke nurturing parental behaviors, but may also elicit a stress response. Deficits in emotional face processing have indeed been associated with parental insensitivity (e.g., Thompson-Booth et al., 2014) and parents at high risk for physical child abuse made more errors in recognizing pictures of emotional faces (Asla, de Paúl, & Pérez-Albéniz, 2011). Moreover, these deficits seem to be reflected in chronic functional alterations in the limbic brain.

Child maltreatment affects the neural circuitry essential to emotional processing (Gee, 2016). Differential neural processing of facial stimuli in maltreated individuals has been observed in the amygdala (Dannlowski et al., 2012; McCrory et al., 2011; Van Harmelen et al., 2013), hippocampus (Maheu et al., 2010), insula (McCrory et al., 2011) and the IFG (Hart et al., 2018). However, while these brain regions are also implicated in caregiving behavior (DeGregorio, 2013; Rilling & Mascaro, 2017; Swain & Ho, 2017), it is unknown whether these neural alterations associated with experienced child maltreatment are associated with parental maltreating behavior as well. Hence, in Chapter 4 of this dissertation it is examined whether altered neural reactivity to (negative) emotional faces is associated with experienced child maltreatment and maltreating parenting behavior and whether it is involved in ITCM.

Next to focusing on brain structure (hippocampal volume) and brain reactivity during the observation of (negative) emotional faces, we also want to examine whether processing social rejection might play a role in ITCM. One of the most important aspects of child maltreatment is parental rejection of needs for attention and nurturance (Bolger & Patterson, 2001; Glaser, 2002), which can occur actively through parental aggression and hostility (abuse) or passively via parental neglect and indifference (Loue, 2005). Being rejected by your own parents can enhance future sensitivity for social rejection in all sorts of situations, including next-generation parent-child interactions (DeWall & Bushman, 2011). Individuals with high levels of rejection sensitivity incline to expect, perceive and overreact to social rejection. They show increased levels of distress and associated neural responses to social rejection. Moreover, rejection sensitivity is associated with the onset and maintenance of psychopathology, such as social anxiety and depression (Rosenbach & Renneberg, 2011).

Research shows that the network of brain areas associated with social rejection and exclusion includes the insula, ACC and mPFC (e.g., Bolling et al., 2011; Cacioppo, Bianchi-Demicheli, Frum, Pfaus, & Lewis, 2012; DeWall et al., 2010; Eisenberger, 2015; Eisenberger, Lieberman, & Williams, 2003; Rotge et al., 2015; Sebastian et al., 2011). Maltreated individuals show altered neural responses to social exclusion in these brain areas (Puetz et al., 2014; 2016; Van Harmelen et al., 2014). Moreover, the same brain areas have also been associated with parenting behavior (Swain and Ho, 2017). These neural networks enable

parents to respond to pain and emotions of their offspring, understand non-verbal signals and infer intentions through empathy and mentalizing (Feldman, 2015; Rilling & Mascaro, 2017). These neural alterations associated with social exclusion might therefore mediate the association between experienced child maltreatment and maltreating parenting behavior. However, to date this is only a hypothesis, since the association between maltreating parenting behavior and neural responses to rejection has not been studied yet.

In Chapter 5 of this dissertation we examine this hypothesis using the Cyberball task, a virtual ball-tossing game, which was performed during the fMRI sessions of the 3G Parenting Study. The Cyberball task is a commonly used paradigm to study the neural correlates of social exclusion (Williams, Cheung, & Choi, 2000). Research shows that individuals of all age groups report increased levels of rejection-related distress after being excluded by two strangers during this task. This rejection-related distress is associated with altered neural reactivity in the ACC, insula and PFC (Eisenberger et al., 2003; Gunther Moor et al., 2012; Masten et al., 2009). Individuals who are rejected during the Cyberball task report higher levels of negative emotions (e.g., sadness, anger) and lower levels of satisfaction with regard to fundamental human needs (e.g., self-esteem, belonging, meaningful existence and control; Abrams, Weick, Thomas, Colbe, & Franklin, 2011; Sebastian, Viding, Williams, & Blakemore, 2010). Moreover, since individual differences in response to social exclusion may depend on the relationship with the person who is excluding (Bernstein, Sacco, Young, Hugenberg, & Cook, 2010; Krill and Platek, 2009; Sacco, Bernstein, Young, & Hugenberg, 2014; Scanlon, 2015) and parents are often perpetrators of child maltreatment (Van Berkel et al., 2020), we differentiated between neural activity following exclusion by one's own mother or child versus strangers and how this is specifically affected in maltreated and maltreating individuals.

ABUSE VERSUS NEGLECT

While examining the impact of trauma we think it is crucial to differentiate between the impact of different types of stressful and traumatic events (see Chapter 2). In the case of child maltreatment we attempt to disentangle the effects of (experiencing and perpetrating) different types of childhood maltreatment, namely child abuse and neglect (see Chapter 3, 4 and 5). We think this is of high importance for several reasons. One of the explanations for the inconsistent findings in the literature regarding the degree of ITCM is the variance in types of maltreatment being examined (Bartlett et al., 2017; Buisman et al., 2020). While most studies investigate childhood maltreatment in general without differentiating between abuse and neglect (Hart & Rubia, 2012; Van IJzendoorn et al., 2020), other studies only focus on abuse, without including child neglect. This also holds for studies into ITCM, of which the majority does not take variation in type of maltreatment in each generation

into account (Kim, 2009). Although neglect is the most prevalent type of maltreatment and long-term effects of neglect seem to be at least as pervasive as those of abuse, it is striking that neglect still is the most hidden and understudied form of childhood maltreatment (e.g., Egeland, 2009; Stoltenborgh, Bakermans-Kranenburg, & Van IJzendoorn, 2013).

Indications for differential effects of different types of child maltreatment are reported in the literature. On a neural level, child abuse and neglect seem to be differentially associated with brain structure and function. For instance, research indicates that different types of maltreatment might be differentially associated with hippocampal volume as reduced hippocampal volume is found to be more strongly associated with experienced childhood abuse than with experienced childhood neglect (e.g., Hanson et al., 2015; Sheridan, Fox, Zeanah, McLaughlin, & Nelson, 2012; Teicher & Samson, 2016). Moreover, abuse and neglect seem to have specific effects on emotion processing and its neural correlates (e.g., Compier-de Block, 2017; Nemeroff, 2016). Therefore, an important aim of our studies in Chapters 3, 4 and 5 is to examine the potential differential effects of (experienced and perpetrated) child abuse and neglect on brain structure (hippocampal volume) and brain function (during emotional face processing and social rejection by family versus strangers).

THE ROLE OF GENDER

Another aim of this dissertation is to study the neglected role of gender with respect to the psychological and neurobiological consequences of trauma. Previous studies show that men and women tend to experience different types of traumatic events (Olff, Langeland, Draijer, & Gersons, 2007; Tolin & Foa, 2008). Interestingly, women are about twice as likely to meet criteria for PTSD than men, even though women are less likely to experience an A1 event. Research shows that men are more likely than women to experience various types of traumatic events, except for sexual and violent trauma (De Vries & Olff, 2009; Tolin & Foa, 2008). Regarding child maltreatment, girls and boys seem to be approximately equally likely to experience maltreatment (except for higher incidence rates of sexual abuse for girls; Thornberry, Knight, & Lovegrove, 2012). However, gender differences are reported regarding the impact of maltreatment, as research indicates more harmful effects of neglect in men compared to women (Teicher et al., 2018). A lot is still unknown about these gender differences, for example whether the increased vulnerability in women to develop PTSD after experiencing A1 events also extends to the experience of non-A1 events and which mechanisms play a role in these gender differences in PTSD development. Some studies suggest that initial responses to trauma may account for gender differences in PTSD (e.g., Irish et al., 2011), but there is still a serious lack of evidence on gender specific appraisal processes of trauma. In Chapter 2 of this dissertation we examine whether the association

between type of experienced (A1 or non-A1) event and PTSD symptoms is different for men and women, and whether anxiety and appraisal of experienced events play a role in potential gender differences with respect to the impact of event type and PTSD symptoms.

On a neurobiological level, gender also seems important to take into account. While gender differences are presented regarding brain structure and function in healthy individuals (e.g., Giedd, Shaw, Wallace, Gogtay, & Lenroot, 2006; Lenroot et al., 2007; Rubia, Hyde, Halari, Giampietro, & Smith, 2010) and individuals with psychopathology (Gur, Gunning-Dixon, Bilker, & Gur, 2002; Valera et al., 2010), gender differences with respect to the neurobiological consequences of trauma (and child maltreatment in particular) received much less attention so far. Most earlier studies regarding the neural consequences of experiencing stress and trauma only include male animals or male human participants (Lupien et al., 2009) or do not examine possible gender effects. There are indications for gender differences regarding the hippocampus, as research indicates that the hippocampus is more sensitive to stress in men than in women (e.g., Cahill, 2006; Everaerd et al., 2012; Samplin, Ikuta, Malhotra, Szeszko, & DeRosse, 2013; Teicher & Samson, 2016; Whittle et al., 2016). Moreover, associations between PTSD and hippocampal volume seem to be driven by women (Logue et al., 2018). Gender differences in the effects of experienced abuse and neglect on hippocampal volume might also be important, since they may result in different neurocognitive and neuropsychological consequences (Teicher et al., 2018), and are therefore examined in Chapter 3.

FOCUS AND OUTLINE OF THE DISSERTATION

The overarching aim of this dissertation is to examine the psychological, neurological and behavioral impact of different types of stressful (non-A1) and traumatic (A1) events, including childhood abuse and neglect. The role of neural correlates of emotional face processing and social rejection in ITCM is investigated using a family study design. Figure 2 offers a graphic presentation of the topics discussed in Chapters 2-5.

In the first part of this dissertation, **Chapter 2,** we examine whether non-A1 and A1 events differ regarding symptom severity and symptom domains of PTSD, whether the association between type of event and PTSD symptoms is different for men and women, and whether anxiety and appraisal of experienced events play a role in potential gender differences with respect to the impact of event type and PTSD symptoms. In the following chapters we describe a combination of structural and functional MRI methods to examine neural correlates of ITCM by making use of an observational (emotional faces task) and experimental paradigm (Cyberball game) in the MRI scanner using a multi-informant, multigenerational family design including participants with a large age range (8-70 years old). In **Chapter 3** we describe a structural MRI study into the associations of bilateral

hippocampal volume with both experienced childhood maltreatment and perpetrated maltreating behavior, enabling the investigation of the potential role of hippocampal volume in ITCM. We differentiate between effects of experienced and perpetrated abuse and neglect and examine the role of gender. **Chapter 4** concerns a functional MRI study examining whether alterations in neural reactivity to emotional faces in the amygdala, hippocampus, IFG and insula are involved in ITCM using an emotional faces task. We examine whether child abuse and neglect show differential effects and investigate whether age moderates associations between neural reactivity to emotional and neutral faces and experienced and perpetrated maltreatment. In **Chapter 5** a second functional MRI study is described in which the impact of experienced and perpetrated abuse and neglect on neural reactivity to social exclusion by strangers versus family members in the insula, dACC and dmPFC is examined using the Cyberball task. We differentiate between effects of (experienced and perpetrated) abuse and neglect and examine whether the effects represent a general sensitivity to exclusion or a specific sensitivity to exclusion by one's own family members. In **Chapter 6** we summarize the results of the studies presented in this dissertation and discuss the implications and recommendations for interventions and future studies.

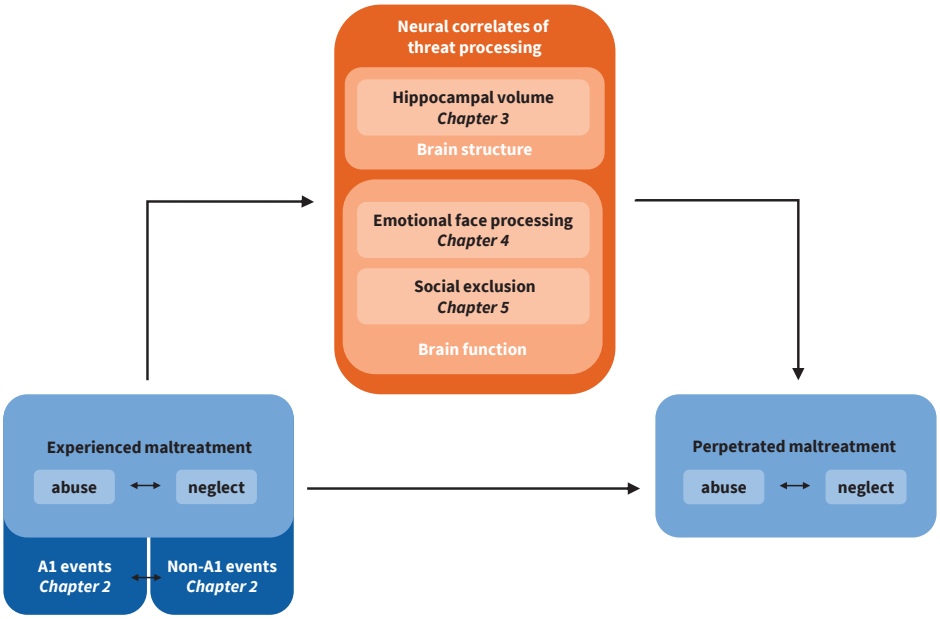

Figure 2. Graphic representation of the topics of the current dissertation.

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