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

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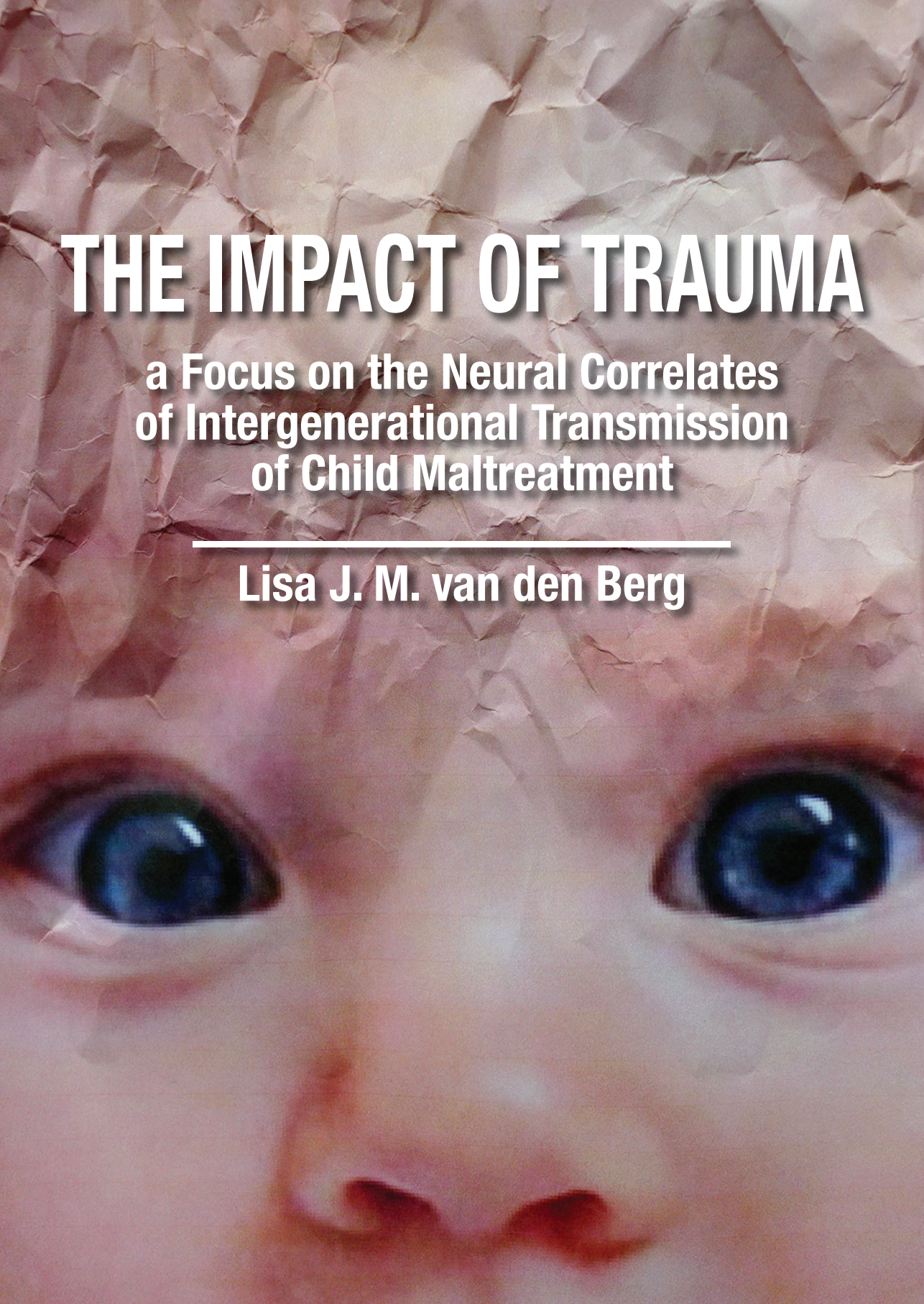
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THE IMPACT OF TRAUMA
a Focus on the Neural Correlates of Intergenerational Transmission of Child Maltreatment
Lisa J. M. van den Berg

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THE IMPACT OF TRAUMA

A focus on the neural correlates of intergenerational transmission of child maltreatment

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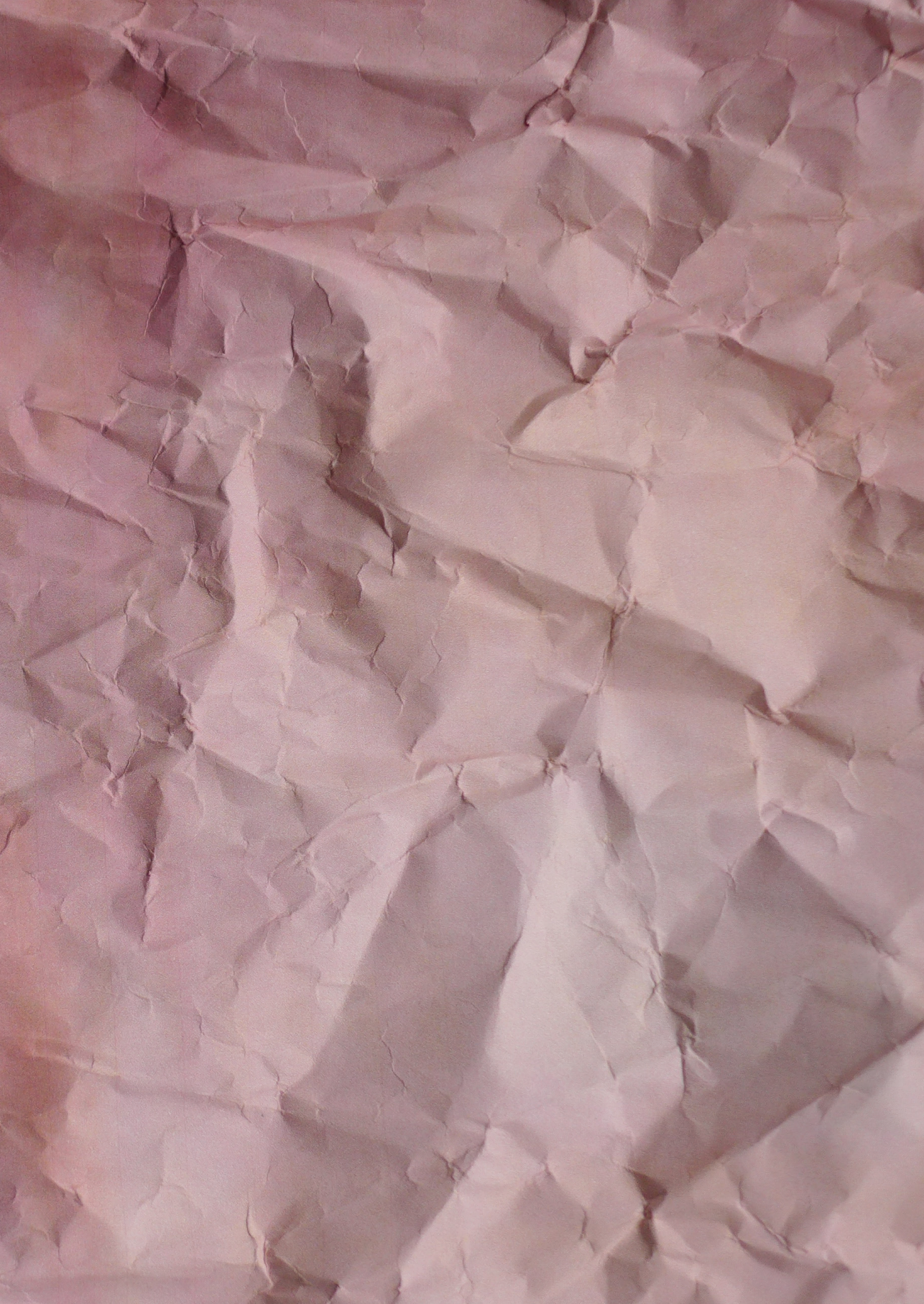
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Voor Samuel

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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.

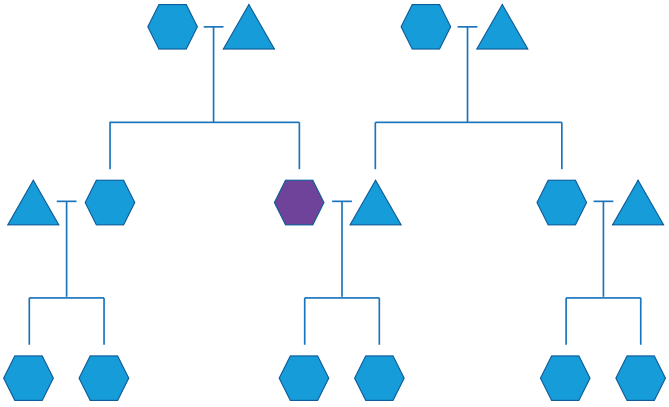


Figure 1. An example of a family tree of participants invited around the target participant (in purple).

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.

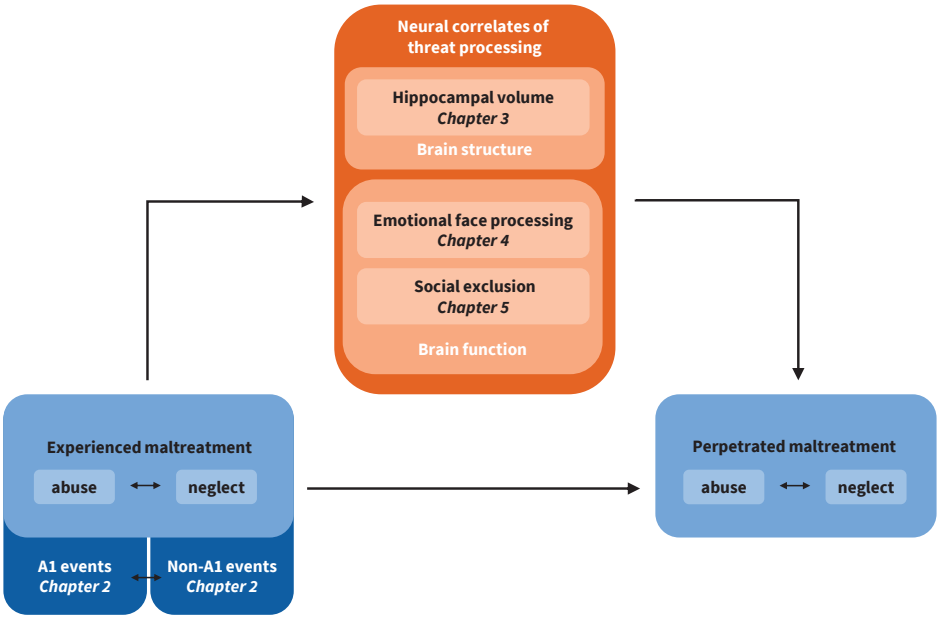


Figure 2. Graphic representation of the topics of the current dissertation.

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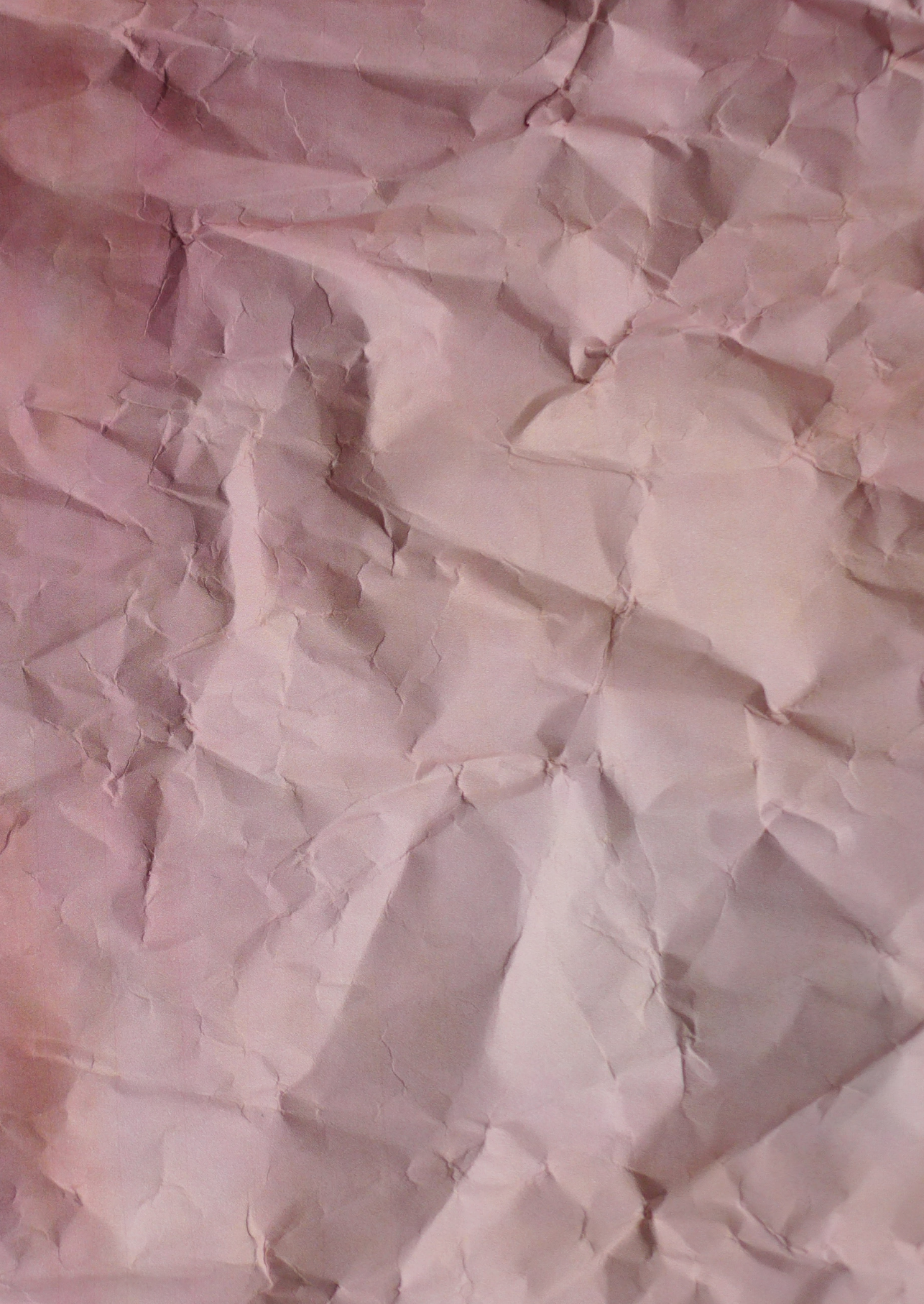
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Chapter 2

A new perspective on PTSD symptoms after traumatic vs stressful life events and the role of gender

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ABSTRACT

Background. There is an ongoing debate about the validity of the A1 criterion of PTSD. Whereas the DSM-5 has opted for a more stringent A1 criterion, the ICD-11 will leave it out as a key criterion.

Objective. Here we investigated whether formal DSM-IV-TR traumatic (A1) and stressful (non-A1) events differ with regard to PTSD symptom profiles, and whether there is a gender difference in this respect.

Methods. This was examined in a large, mostly clinical sample from the Netherlands Study of Depression and Anxiety (n = 1433). Participants described their most bothersome (index) event and were assigned to either an A1 or non-A1 event group according to this index event.

Results. Remarkably, in men PTSD symptoms were even more severe after non-A1 than A1 events, whereas in women symptoms were equally severe after non-A1 and A1 events. Moreover, while women showed significantly higher PTSD symptoms after A1 events than men (29.9 versus 15.4% met PTSD criteria), there was no gender difference after non-A1 events (women: 28.2%; men: 31.3%). Furthermore, anxiety and perceived impact were higher in women than men, which was associated with PTSD symptom severity.

Conclusion. In sum, while women showed similar levels of PTSD symptoms after both event types, men reported even higher levels of PTSD symptoms after non-A1 than A1 events. These findings shed a new light on the role of gender in PTSD symptomatology and the clinical usefulness of the A1 criterion.

Keywords: PTSD; aetiology; gender; traumatic events; life events

BACKGROUND

Post-Traumatic Stress Disorder (PTSD) is one of only a few disorders in the DSM (American Psychiatric Association, 2013) that require an aetiological factor (a traumatic event) for its diagnosis. In the DSM-IV-TR this so-called A1 criterion involved 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). In the DSM-5, the 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. During the last decades there has been an ongoing debate about the validity and clinical usefulness of the A1 criterion. One of the first critiques is that other (non-A1) stressful life events can also cause PTSD (Breslau & Davis, 1987). Since this influential paper, several studies have reported that stressful non-A1 events are associated with similar or even higher rates of PTSD symptoms than A1 events (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), questioning the constricted definition of traumatic A1 events. In this regard, in contrast to the DSM-5, the ICD-11 will differentiate less between effects of formal DSM traumatic (A1) events and other (non-A1) stressful life events (World Health Organization), and diagnosis of PTSD will mainly be based on PTSD symptom presentation (Maercker et al., 2013; World Health Organization; Vermetten, Baker, Jetly, & McFarlane, 2016). Hence, this calls for a renewed discussion on the role of stressful life events in the development of PTSD.

Furthermore, women are approximately twice as likely to meet criteria for PTSD than men, even though women are less likely to experience an A1 event (Olff, Langeland, Draijer, & Gersons, 2007; Tolin & Foa, 2008). Men and women tend to experience different types of A1 events but, even after controlling for type of experienced A1 event, the gender differences in PTSD prevalence remain (Christiansen & Hansen, 2015; Moser, Hajcak, Simons, & Foa, 2007; Tolin & Foa, 2008). It is still unknown whether the increased vulnerability in women to develop PTSD after experiencing A1 events also extends to the experience of non-A1 events. Earlier studies that examined the association between A1 versus non-A1 events and PTSD symptom severity only investigated women (e.g. Anders et al., 2011; Cameron et al., 2010; Roberts et al., 2012) or did not investigate gender differences (e.g. Gold et al., 2005).

Little is known about the mechanisms behind gender differences in PTSD development. A possible explanation may be that women experience (A1 and non-A1) stressful events as more anxiety provoking. Anxiety sensitivity predicts PTSD symptom severity and it is suggested that this association is stronger for women (Feldner, Zvolensky, Schmidt, & Smith, 2008; Marshall, Miles, & Steward, 2010). Such peri-traumatic processes, including

appraisal processes concerning the trauma, play an important role in the development of PTSD after trauma (Ozer, Best, Lipsey, & Weiss, 2003). Subjective measures of distress or impact of experienced events are often even better in predicting PTSD symptoms than objective measures of danger during events (McNally, 2003). Some studies indeed suggest that these initial responses to trauma may account for gender differences in PTSD (e.g. Irish et al., 2011), but a review by Olff et al. (2007) emphasizes that there is a serious lack of evidence on gender specific appraisal processes of trauma.

Lastly, co-morbidity between PTSD and other psychopathology is common, with the majority of PTSD patients meeting criteria for at least one other psychiatric disorder (e.g. Brady, Killeen, Brewerton, & Lucerini, 2000; Flory & Yehuda, 2015). However, to date it is unclear whether comorbid psychopathology heightens PTSD sensitivity and whether this is related to gender differences in PTSD symptoms.

The current study is the first to examine the associations between type of events and PTSD symptom severity by specifically focusing on how gender may affect the impact of those events using a large, mostly clinical sample. In 427 men and 1006 women it will be examined whether (1) non-A1 and A1 events differ regarding symptom severity and symptom domains of PTSD, (2) the link between type of event and PTSD symptoms is different for men and women, and (3) anxiety and appraisal of experienced events play a role in potential gender differences with respect to the impact of event type and PTSD symptoms.

METHOD

Study design and population

Data for the present study were drawn from the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal cohort study among 2981 participants at baseline. The NESDA sample consists of individuals with a past or current depression and/or anxiety disorder, and healthy controls. General inclusion criteria were an age of 18 through 65 years during baseline assessment and being fluent in Dutch. The presence of clinically overt other psychiatric conditions that required specific other treatment (e.g. obsessive-compulsive disorder, bipolar disorder, PTSD, psychotic or severe substance use disorder) was an exclusion criterion and these disorders were not included in the NESDA study, because the primary focus of the study was on depressive and anxiety disorders (see also Spinhoven, Penninx, Van Hemert, De Rooij, & Elzinga, 2014). Since there was no active screening for PTSD, PTSD was still quite prevalent (27.8% in our sample [n = 398: 108 men and 290 women]; 6.7% in the total NESDA sample). The study protocol was approved centrally by the Ethical Review Board of the VU University Medical Center Amsterdam and by local review boards of each participating centre. All respondents provided written informed consent. Further details about NESDA are provided elsewhere (Penninx et al., 2008).

Four years after the baseline assessment (T4) a face-to-face assessment was conducted by trained research staff with a response rate of 80.6% (*n* = 2402), including the Life Events Checklist (LEC; see below) and a clinical interview on PTSD symptoms (PSS-I; see below). Of all participants who were interviewed with the LEC (*n* = 2402), *n* = 2165 participants indicated that they experienced an A1 or stressful non-A1 event. Of this group, *n* = 1156 participants reported an A1 event as their index event, whereas *n* = 1000 participants reported a non-A1 event.

Measures

Post-traumatic stress symptoms

Administration of the PTSD Symptom Scale - Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993) was preceded by the Life Events Checklist (LEC; Weathers, Keane, & Davidson, 2001) in order to assess possible exposure to A1 or non-A1 events according to the DSM-IV-TR (American Psychiatric Association, 2000). The LEC describes 16 potentially traumatic A1 events and participants were asked whether they had experienced any of these events ever during their lives. Moreover, participants were asked whether they had experienced any of the following four non-A1 events (the death of someone close to you [other than sudden violent or unexpected death of someone close to you], a severe physical illness, relational problems, problems at work), and whether they had experienced any additional other impactful (A1 or non-A1) events ever in their lives. Next, participants were asked to select one of all reported (A1 and non-A1) events as their most bothersome experience (i.e. index event; 'please select your most bothersome event from all previously mentioned events') and when that event started and ended.

The PSS-I followed with three screening questions asking whether during the past five years (or during a shorter time period in case the event was more recent) the participant had been bothered by intrusive thoughts or images, avoidance of event related cues or heightened arousal related to the index event. When one of these three screening questions was answered positively, the full PSS-I was administered. In that case, participants were asked how often they had experienced each of the 17 criteria on the three subscales for PTSD as listed in the DSM-IV-TR (i.e. five items on re-experiencing [Cluster B], seven on avoidance/numbing [Cluster C] and five on arousal [Cluster D]) during a period of four weeks of the past five years when symptoms related to the index event were most severe.

Presence of a PTSD diagnosis was based on the DSM-IV-TR symptom criteria using the criteria of Brewin et al. (Brewin, Andrews, & Rose, 2000; Engelhard, Van Den Hout, Arntz, & McNally, 2002). A symptom was scored as present when experienced at least 2–4 times a week. This is a more conservative scoring than the scoring of Foa et al. (Foa, Cashman, Jaycox, & Perry, 1997; Foa et al., 1993) in which a symptom is scored as present if it occurred at least once a week (or less). Cronbach's α was satisfactory-to-good: re-experiencing (0.73);

avoidance/numbing (0.74); arousal (0.71); and total PSS-I scale (0.88). Sensitivity of the PSS-I has been shown to be good, namely .88 (Foa et al., 1993; Foa & Tolin, 2000).

For the current study, all events mentioned by participants in the context of the LEC (including all impactful events that were additionally mentioned) were classified as A1 or non-A1 events according to the DSM-IV-TR by two independent raters using a coding system (inter-rater reliability was high: $\kappa = 0.86$, see Supplement). The coding system consisted of the 16 A1 events of the LEC, 20 types of non-A1 events (e.g. relational problems, problems at work), and a residual 'exclusion' category (e.g. own psychological symptoms [e.g. burn-out, depression]), not included in the analyses. Next, participants were assigned to either the A1 or non-A1 event group according to their index event.

Anxiety during event and perceived impact of the index event

During the PSS-I participants were also asked to indicate the degree of anxiety during the index event and the perceived impact of this event on their lives during and directly after exposure on 10-point scales ranging from '1' to '10' (see Spinhoven, Penninx, Krempeniou, Van Hemert, & Elzinga, 2015; Spinhoven et al., 2014).

Psychopathology

Presence of DSM-IV-TR (American Psychiatric Association, 2000) based depressive and anxiety disorders was established using the Composite Interview Diagnostic Instrument (CIDI, version 2.1), a standardized diagnostic interview that is used worldwide for assessing psychiatric diagnoses with high inter-rater reliability, high test-retest reliability and high validity (Wittchen, 1994). We determined the five-year prevalence of depressive and anxiety disorders based on the T0, T2 and T4 assessments of the NESDA study to obtain a five-year recency diagnosis (comparable to the five-year recency PTSD diagnosis of the PSS-I): 77.9% of our sample fulfilled the criteria of an anxiety or depressive disorder during the five-year period before administration of the PSS-I (see Table 1).

ANALYSES

Log PSS-I scores (PSS-I subscale and total scores) were calculated to normalize the data and were used as main outcome variables. Untransformed PSS-I scores are presented in Table 1, Figure 1 and Table 2.

To examine possible main effects for event type (A1 versus non-A1 events) and gender, and interaction effects between event type and gender, an ANOVA and MANOVA were conducted. Moreover, ANOVA's were conducted to investigate the role of anxiety during and perceived impact after exposure to the index event. Statistical analyses were run using SPSS version 21 at alpha .05, with a Bonferroni correction for all analyses.

Table 1. Demographics and PSS-I scores of all included participants (n = 1433) and main and interaction effects for event type and gender.

Variables	Index event: A1 event (n = 573)		Index event: non-A1 event (n = 860)		Main effect event	Main effect gender	Interaction event x gender
	Men	Women	Men	Women			
Gender distribution[a]	n = 162; 28.3%	n = 411; 71.7%	n = 265; 30.8%	n = 595; 69.2%	-	p < 0.001	n.s.
Age (in years)[b]	43.96 (13.16)	41.55 (12.29)	43.44 (12.20)	40.89 (12.58)	n.s.	p = 0.001	n.s.
Educational level (in years)	12.16 (2.89)	12.02 (3.10)	12.69 (3.38)	12.68 (3.33)	p = 0.002	n.s.	n.s.
Years since index event	11.16 (14.60)	12.18 (14.35)	9.24 (10.84)	8.70 (10.09)	p < 0.001	n.s.	n.s.
% with psychopatho-logy[c]	71.0%	82.7%	74.0%	77.6%	n.s.	n.s.	n.s.
% meeting PTSD B, C, and D criteria[d]	15.4%	29.9%	31.3%	28.2%	p = 0.006	p < 0.001	p = .002
PSS-I Total score[e]	10.12 (9.82)	14.24 (11.93)	13.91 (11.39)	13.41 (10.27)	p = 0.007	p = 0.005	p = 0.005
PSS-I score: Subscale A Intrusions[e]	2.94 (3.70)	4.25 (4.12)	3.72 (3.88)	4.07 (3.73)	p = 0.03	p < 0.001	n.s.
PSS-I score: Subscale B Avoidance[e]	3.96 (4.37)	5.30 (5.21)	5.77 (5.08)	5.13 (4.60)	p = 0.001	n.s.	p = 0.006
PSS-I score: Subscale C Arousal[e]	3.22 (3.40)	4.68 (4.12)	4.36 (3.99)	4.23 (3.75)	n.s.	p = 0.005	p = 0.004
PSS-I score: anxiety during event[e]	5.62 (3.36)	6.67 (3.19)	5.46 (3.06)	5.80 (3.03)	p = 0.006	p < 0.001	n.s.
PSS-I score: perceived impact of event[e]	8.19 (2.03)	8.83 (1.56)	8.17 (1.68)	8.45 (1.51)	p = 0.04	p < 0.001	n.s.

PSS-I = PTSD Symptom Scale - Interview version; PTSD = Post-Traumatic Stress Disorder.

[a]Gender distribution: 0 = men; 1 = women. [b]Mean age in years during the PSS-I is reported. [c]Psychopathology (depression and anxiety) during 5 years before administration of the PSS-I as measured with the CIDI is reported. [d]PTSD B, C and D according to the Brewin & Engelhard criteria. [e]Means and SD's of the untransformed raw PSS-I scores are reported.

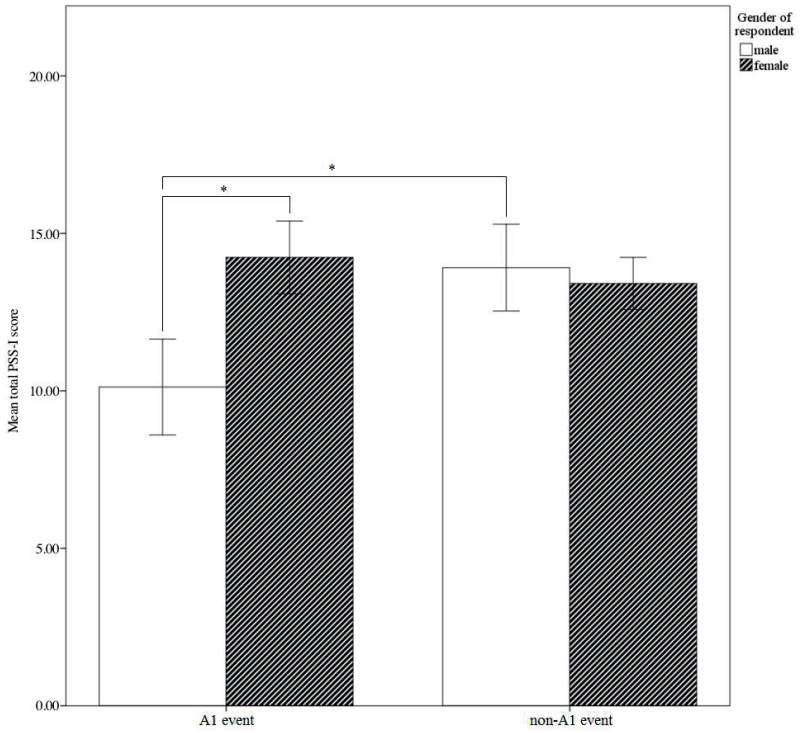


Figure 1. Mean total PSS-I scores for men and women per type of event.
Untransformed PSS-I scores are presented.

RESULTS

Participants and events

Of all participants with an A1 index event, 49.6% (*n* = 573) indicated on the screening questions of the PSS-I that they were bothered by intrusive thoughts or images, avoidance of event related cues and/or heightened arousal related to the index event during the past five years (or during a shorter time period in case the event was more recent) versus 86.0% (*n* = 860) of all participants with a non-A1 index event. The complete PSS-I was administered in these cases, hence this sample was selected for the current study (*n* = 1433). See Table 1 for demographics and mean (SD) PSS-I scores.

The most commonly reported A1 index event for both men and women was the sudden unexpected death of someone close. A life-threatening illness or injury was the second most frequently reported A1 index event for men, whereas sexual assault was the second most commonly reported A1 event for women. Regarding non-A1 index events, both men and women reported a severe physical illness and relational problems most frequently (see Table 2).

Table 2. Mean total PSS-I scores of all participants for whom the PSS-I was completed.

	n		Mean PSS-I scores[a]	
	men	women	men	women
A1 index events				
Natural disaster (for example flood, hurricane, earthquake)	1	1	2.00	0.00
Fire or explosion	4	6	21.75	18.83
Transportation accident (for example car accident, train wreck, plane crash)	9	33	12.00	10.58
Serious accident at work, home or during recreational activity	8	9	10.25	10.33
Exposure to toxic substance (for example dangerous chemicals, radiation)	2	1	13.00	0.00
Physical assault (for example being attacked, hit or kicked)	14	41	6.11	18.68
Assault with a weapon (for example being shot and/or stabbed or threatened with a knife, gun, or bomb)	10	5	3.50	17.00
Sexual assault (rape, attempted rape, made to perform any type of sexual act through force or threat of harm)	8	58	17.50	21.28
Other unwanted or uncomfortable sexual experience	4	26	6.50	14.22
Combat or exposure to a war-zone (in the military or as a civilian)	2	2	3.00	12.50
Captivity (for example being kidnapped, abducted, held hostage, prisoner of war)	0	4	-	19.00
Life-threatening illness or injury	22	38	10.55	13.61
Severe human suffering	19	42	11.26	13.19
Sudden, violent death of someone close to you (for example homicide, suicide)	21	33	9.52	12.12
Sudden, unexpected death of someone close to you	38	111	10.42	11.29
Serious injury, harm or death caused by you	0	1	-	16.00
Non-A1 index events				
Death of someone close to you	45	127	6.04	10.09
Severe physical illness (of you or someone close to you)	67	162	13.34	11.99
Relational problems	65	129	15.38	15.95
Problems at work	51	66	20.48	16.94
Miscarriage, abortion, unfulfilled desire to have children, problems during childbirth, unwanted pregnancy	2	20	12.00	11.95
Death of someone not close to you (for example client, student)	1	1	15.00	2.00
Family problems: decreased contact	2	8	11.50	7.13
Family problems: psychological problems	6	13	14.50	13.62
Family problems: rest	13	29	11.77	14.90
Family problems: divorce of parents	4	9	7.25	9.33
Non-family problems: decreased contact	0	1	-	9.00
Non-family problems: psychological problems	1	3	0.00	17.33
Non-family problems: rest	1	4	7.00	19.00
Financial problems	0	3	-	10.33

Table 2. Mean total PSS-I scores of all participants for whom the PSS-I was completed. (continued)

	n		Mean PSS-I scores[a]	
	men	women	men	women
Burglary, housebreaking	1	2	32.00	22.50
Moving	0	2	-	25.00
Bullying and stalking	3	10	24.33	17.60
Being threatened or threatening of someone close to you	1	1	20.00	22.00
Emotional neglect	0	1	-	26.00
Psychological and emotional abuse	2	4	7.00	25.50
Rest				
Psychological symptoms of the participant (for example burn-out, depression)	10	4	19.53	16.75

PSS-I: PTSD Symptom Scale – Interview version

[a]Means of the original PSS-I scores are reported

PSS-I symptoms

The ANOVA with the PSS-I total score as dependent variable, shows a main effect for event type ($F(1, 1429) = 7.41$, $p = .007$, partial $\eta 2 = 0.005$) and gender ($F(1, 1429) = 7.95$, $p = .005$, partial $\eta 2 = 0.006$). Moreover, these two main effects are specified by an interaction for type of event and gender ($F(1, 1429) = 8.02$, $p = .005$, partial $\eta 2 = 0.006$). Men and women show similar levels of PTSD symptoms after non-A1 events, whereas women show significantly higher PTSD symptoms after A1 events than men. Moreover, men show significantly higher PTSD symptoms after non-A1 events, whereas women show similar levels of PTSD symptoms after both types of events (see Figure 1).

PSS-I subscales

The MANOVA with the PSS-I subscale scores as dependent variables and type of event and gender as fixed factors, using Wilks's statistic, shows similar interaction between type of event and gender with respect to avoidance ($\Lambda = 0.99$, $F(1,1426) = 7.66$, $p = .006$, partial $\eta^2 = 0.005$) and arousal ($\Lambda = 0.99$, $F(1,1426) = 8.18$, $p = .004$, partial $\eta^2 = 0.006$). Men whose index event was a non-A1 event report higher levels of avoidance and arousal than men whose index event was an A1 event, whereas women do not report any significant differences in avoidance or arousal after both types of events. Furthermore, participants report higher intrusion scores after experiencing non-A1 events than A1 events as index event ($\Lambda = 0.99$, $F(1,1426) = 4.69$, $p = .03$, partial $\eta^2 = 0.003$) and women report higher intrusion scores than men ($\Lambda = 0.99$, $F(1,1426) = 17.50$, $p < .001$, partial $\eta^2 = 0.01$). No interaction was found for intrusion scores ($p > .05$).

Potential confounders

We also investigated whether several possible confounders might explain the interaction effect for type of event and gender on PSS-I total scores (see Supplement for full analyses). In short, the interaction effect for type of event and gender became somewhat smaller but remained significant when we repeated our analyses leaving out all sexual assault (interaction type of event x gender: p = .03, partial η^2 = 0.004). Moreover, this was also the case when adding depression/anxiety diagnoses as a predictor (main effect depression/anxiety: p < .001, partial η^2 = 0.082; interaction type of event x gender: p = .04, partial η^2 = 0.003), indicating that our findings cannot be explained by differences in comorbid depression and/or anxiety diagnoses. Furthermore, when we added the number of years since the event (main effect on PTSD symptoms: p = .76) and the number of recent negative life events in the five years preceding the administration of the PSS-I (main effect on PTSD symptoms: p < .001, partial η^2 = 0.027) as covariates the interaction effect for type of event and gender remained significant (interaction type of event x gender for number of years since the event: p = .02, partial η^2 = 0.004; interaction type of event x gender for number of recent negative life events: p = .008, partial η^2 = 0.005). To examine whether our results are specific for events that happened a long time ago we repeated our main analysis for participants who experienced their index event in the last five years (n = 715). The finding that life events are at least as burdensome as A1 events holds up (no main effect for event: p = .11), but the finding that men report significantly more symptoms on non-A1 than A1 events is less clear for more recent events (main effect gender: p = .04, partial η^2 = 0.006, but no interaction effect between type of event and gender: p = .50). Coding all index events according to the DSM-5 did not change our main findings either (see Supplement).

The role of anxiety and perceived impact

The ANOVA with gender and type of event as independent factors showed that both men and women report significantly higher levels of anxiety during exposure to A1 compared to non-A1 events (F(1,1428) = 7.68, p = .006, partial η^2 = 0.005) and also higher levels of perceived impact after exposure to A1 compared to non-A1 events (F(1,1427) = 4.12, p = .04, partial η^2 = 0.003; see Table 1). Overall, women report higher anxiety scores than men (F(1,1428) = 14.27, p < .001, partial η^2 = 0.01), and also higher levels of perceived impact of the events than men (F(1,1427) = 22.89, p < .001, partial η^2 = 0.02). There is no interaction effect between type of event and gender for the degree of anxiety (p = .05) nor perceived impact (p = .06), see Table 1.

Additionally, levels of anxiety and impact were more strongly associated with PTSD symptom severity for women (anxiety: r = .30, p < .001; impact: r = .31, p < .001) compared to men (anxiety: r = .19, p = .01; impact: r = .20, p = .01) after A1 events, but after non-A1 events associations of anxiety and impact with PTSD symptom severity were comparable

for men (anxiety: $r = .26$, $p < .001$; impact: $r = .28$, $p < .001$) and women (anxiety: $r = .32$, $p < .001$; impact: $r = .30$, $p < .001$).

DISCUSSION

Main findings

The DSM (American Psychiatric Association, 2013) requires the experience of a traumatic A1 event for the diagnosis of PTSD, thereby aiming to select only the most severe cases of PTSD. In contrast, in line with previous research (e.g. Anders et al., 2011; Gold et al., 2005; Mol et al., 2005) and the ICD-11 approach (World Health Organization), the current study shows in a large, mostly clinical sample that PTSD symptoms were equally or more severe in participants reporting non-A1 events than A1 events. Remarkably, 86.0% of all participants from the non-A1 event group indicated to be bothered by intrusions, avoidance of event related cues and/or heightened arousal related to the index event during the past five years versus 50% of the A1 event group. More specifically, men who experienced a non-A1 index event, such as a severe physical illness or relational problems, showed significantly higher PTSD scores than men whose index event was an A1 event, particularly in terms of avoidance and arousal symptoms. For women PTSD symptom severity was the same in both event groups. Moreover, it was striking that whereas in the A1 event group women showed significantly higher PTSD symptoms than men (29.9 versus 15.4% met PTSD B, C and D criteria), in line with previous studies (e.g. Tolin & Foa, 2008), in the non-A1 event group there were no gender differences in PTSD symptoms (women: 28.2%; men: 31.3%).

Most of the earlier studies that investigated the association between A1 versus non-A1 events and the severity of PTSD symptoms only investigated female participants or did not report on gender differences (e.g. Anders et al., 2011; Cameron et al., 2010; Roberts et al., 2012). The only study that did investigate gender differences reported that different types of traumas might be associated with differences in PTSD symptoms in women but not in men, but was limited by using a non-clinical sample and investigating a limited number of events (Lancaster, Melka, Rodriguez, & Bryant, 2014). In contrast, in the current study women did not report differences in the severity of PTSD symptoms on any of the symptom clusters per type of event, while men reported more intrusions, arousal and especially higher levels of avoidance symptom severity after non-A1 versus A1 events.

Regarding the type of reported non-A1 index events, we found that for both men and women severe physical illnesses, relational problems and the death of someone close are among the most commonly reported non-A1 index events. This is in line with previous research (e.g. Mol et al., 2005; Roberts et al., 2012). The high levels of PTSD symptoms after such events could be explained by the fact that interpersonal, relational events are

particularly distressing and predictive of PTSD symptoms (Anders et al., 2011; McNally & Robinaugh, 2011), underscoring the need for a new perspective on PTSD symptoms after stressful versus traumatic life events.

We tried to examine the underlying mechanism of the gender-related differences in PTSD symptomatology. We found that comorbid anxiety and/or depression heightens PTSD sensitivity, but this was not related to gender differences in PTSD symptoms. Moreover, a higher number of recently experienced negative life events was also associated with higher levels of PTSD symptoms but this could not explain the gender differences either. Finally, we aimed to investigate whether anxiety and appraisal of non-A1 and A1 events are involved in the gender-related differences in PTSD symptomatology. Overall, participants reported significantly higher levels of anxiety and perceived impact after exposure to A1 compared to non-A1 events. Moreover, women reported higher anxiety and perceived impact of either events than men. This is in line with studies showing that women report higher levels of perceived life threat after traumatic A1 events which is predictive of posttraumatic distress (Irish et al., 2011) and might be associated with lower levels of perceived control in women compared to men after A1 events (e.g. Mak, Blewitt, & Heaven, 2004; Olff et al., 2007). Furthermore, anxiety sensitivity more strongly predicts PTSD symptom severity in women (Feldner et al., 2008). However, even though higher anxiety and perceived impact in women may partly explain the higher PTSD scores in women than in men after experiencing A1 events, this cannot explain the lack of gender differences in PTSD symptoms after non-A1 events. Moreover, this is also at odds with the finding that men experience more PTSD symptoms after non-A1 versus A1 events. Similarly, levels of anxiety and impact were more strongly associated with PTSD symptom severity for women compared to men after A1 events, but not after non-A1 events, showing differential psychological processes may underlie the development of PTSD symptoms after non-A1 versus A1 events in men and women. While the presence of comorbid depression and/or anxiety was clearly associated with higher PTSD levels, this could not explain the gender differences in PTSD symptom severity.

The use of different stress-regulating coping strategies after the experience of A1 and non-A1 events in men and women might help explain our findings. It is remarkable that men report particularly high levels of avoidance after non-A1 events compared to A1 events. Avoidance refers to cognitive, emotional, and behavioural avoidance strategies and studies show that avoidance coping is prospectively associated with PTSD symptoms (e.g. Hayes, Wilson, Gifford, Follette, & Strosahl, 1996). Given the role of gender in the socialization of emotion processing and regulation (Root & Denham, 2010), it is possible that men show more avoidance after non-A1 life events compared to A1 events because it is less socially accepted for men to be affected by events that are not officially classified as traumatic. Higher levels of peri-traumatic dissociation in men after non-A1 events might also play a role, since peri-traumatic dissociative symptoms are associated with increased

PTSD risk as well (Bryant & Harvey, 2003; Fullerton et al., 2001), although we did not measure dissociation in the current study. The use of a longitudinal design is recommended for future studies to more precisely examine the potential underlying mechanisms (e.g. gender-specific coping strategies) driving the gender differences we found, while focusing on DSM-5 PTSD symptom presentation instead of the A1 criterion.

Strengths and limitations of our study

A main strength of the current study is the large, mostly clinical sample of 427 men and 1006 women with careful assessments of comorbid psychopathology, based on structured interviews by trained researchers. This made it possible to reliably investigate gender differences in PTSD symptom severity and to carefully investigate the role of comorbid depression and/or anxiety in the context of the gender discussion, which has not been addressed in previous studies. Moreover, given the high comorbidity between PTSD and other psychopathological conditions, specifically depression (21–94%) and other anxiety disorders (39–97%; Ginzburg, Ein-Dor, & Solomon, 2010; Perkonigg, Kessler, Storz, & Wittchen, 2000), a clinical sample as the current one is representative of the general PTSD population.

A first limitation of the current study is that participants were not explicitly asked to identify *all* experienced stressful life events so that we were not able to take into account the total number of experienced A1 and non-A1 events. Moreover, we have no specific information about the amount of time between exposure to the index event and the period of four weeks when symptoms were most severe. A next limitation is that individuals with a primary severe diagnosis of PTSD or substance use disorder (SUD) that required specific other treatment were initially omitted from the NESDA study. However, because there was no active screening for PTSD or SUDs, PTSD and SUD was still quite prevalent in our sample (PTSD: 27.8%) and in the total NESDA sample (6.7%; Boschloo et al., 2011; Manthey et al., 2012; Spinhoven et al., 2014), and therefore we expect little impact on our results. Moreover, peri-traumatic anxiety and perceived impact were measured with one-item interview questions only and future studies may profit from a more comprehensive assessment of these constructs. Furthermore, since we used a between-subject design, pre-existing differences between the A1 and non-A1 event group may have affected the outcomes as well. For instance, participants in the A1 event group had a somewhat lower educational level. However we controlled for this, and this does not seem to have affected our results. Nonetheless, there could have been other group differences we did not account for. Finally, the experience of index events and PTSD symptom severity was measured retrospectively, which may have affected the recall of events and symptoms (i.e. omission and biased retrieval) in some participants. This potential recall bias might be dependent on gender. For instance, women might report more traumatic events perpetrated by someone close, whereas men might report more events perpetrated by someone not so

close (Friedrich, Talley, Panser, Fett, & Zinsmeister, 1997; Goldberg & Freyd, 2006). Again, prospective research would be important to explore this potential bias.

CONCLUSIONS

Altogether, these findings indicate that stressful life events that are not classified as traumatic, according to the DSM A1 criterion, can generate at least the same levels of PTSD symptom severity as A1 events. Several traumatic events defined as A1 events in the DSM-IV-TR (American Psychiatric Association, 2000), for example a serious illness of the self or a close friend or family member and a sudden (non-violent) unexpected death due to natural causes, were excluded in the DSM-5. As a result, some individuals who met the DSM-IV-TR symptom criteria of PTSD do not meet the DSM-5 PTSD criteria (e.g. Hoge, Riviere, Wilk, Herrell, & Weathers, 2014; Kilpatrick et al., 2013). Our study emphasizes that these stressful event types can cause similar levels, and for men even higher levels, of symptoms and suffering in daily functioning. This questions the rationale behind these changes, and the definition of the A1 criterion in general. It is questionable whether individuals with at least as high PTSD symptom severity but no official A1 criterion should be excluded from treatment, or from reimbursement of treatment. In fact, based on the current findings and in line with the approach of the ICD-11, we recommend clinicians to pay attention to PTSD symptom profiles rather than the strict definition of the A1 criterion, to prevent highly symptomatic individuals being excluded from treatment. Furthermore, our results underscore the impact of life events in general and the adjustment problems that men and women may encounter after such life events. People report high levels of anxiety during life events and high levels of perceived impact after exposure to these life events. Moreover, a higher number of recent negative life events was also associated with higher levels of PTSD symptoms. Since negative life events are highly prevalent, studying factors associated with successful adaptation to those events could help make society more resilient and prevent stress and suffering in daily life. Frequently reported stressful life events, for example relational and work problems, seem to be on a more practical and controllable level than most A1 events such as the sudden, unexpected death of someone close. Therefore, it would be interesting to examine whether treatments for adjustment to specific types of life events, for instance focused on coaching and coping, would be more effective than exposure-based trauma treatments.

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DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

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SUPPLEMENT

METHOD

Study design and population

A total of 673 other participants who mentioned that they experienced an A1 (*n* = 560) or non-A1 (*n* = 113) index event did not experience this event as bothersome during the last five years according to the screening questions, and therefore the other PSS-I questions were not administered. Nine participants reported several events, but did not select their index event and did not answer the screening questions. Other participants indicated that they did experience an A1 (*n* = 23) or non-A1 (*n* = 27) index event, but did not answer the screening and following PSS-I questions. Furthermore, *n* = 18 participants were excluded from further analyses because they either stated that their index event was the experience of their own psychopathology (burn-out, depression, etc.; *n* = 14) or listed an event that did not fit into the A1 or non-A1 event category (*n* = 4).

Measures

Post-traumatic stress symptoms

The list of non-A1 events of the coding system was composed based on the most frequently mentioned non-A1 events by participants to enable classification of all events into one of the three categories. Some participants (of the final participant group) mentioned more than one event as index event (*n* = 99). When an A1 event was mentioned as one of these events, they were assigned to the A1 event group. In all other cases, they were allocated to the non-A1 event group.

Correlation coefficients between PSS-I scales were as follows: re-experiencing with avoidance/numbing = 0.58; re-experiencing with arousal = 0.56; and avoidance/numbing with arousal = 0.63.

RESULTS

Potential confounders

To check whether the higher severity of PTSD symptoms for women in the A1 event group was mainly driven by higher frequency of sexual assault, we repeated our analyses leaving out all sexual assault. The interaction effect for type of event and gender remained significant ($F(1, 1333) = 4.87$, $p = .03$, partial $\eta^2 = 0.004$). We also investigated the potential effect of five-year prevalence of psychopathology (assessed with the CIDI, see Table 1) by performing an ANOVA with the PSS-I total score as dependent variable and type of event,

gender and the presence/absence of anxiety and/or depression diagnoses as fixed factors. Again, the interaction effect for type of event and gender remained significant ($F(1, 425) = 4.07$, $p = .04$, partial $\eta^2 = 0.003$), with psychopathology as a significant predictor ($F(1, 1425) = 126.65$, $p < .001$, partial $\eta^2 = 0.082$). There was no three-way interaction of type of event with gender and psychopathology ($F(1, 1425) = 0.079$, $p = .78$, partial $\eta^2 = 0.000$). These results indicate that our findings cannot be explained by differences in comorbid depression and/or anxiety diagnoses. Furthermore, non-A1 events took place more recently than the A1 events. When we added the number of years since the event as a covariate the main effect for type of event ($F(1, 1308) = 8.49$, $p = .004$, partial $\eta^2 = 0.006$) and interaction effect for type of event and gender also remained significant ($F(1, 1308) = 5.50$, $p = .02$, partial $\eta^2 = 0.004$). Moreover, when we added the number of negative life events in the past five years as reported on the LTE-Q (Brugha, Bebbington, Tennant, & Hurry, 1985; main effect on PTSD symptoms: $p < .001$, partial $\eta^2 = 0.027$) as a covariate the main effect for type of event ($F(1, 1427) = 9.27$, $p = .002$, partial $\eta^2 = 0.006$) and interaction effect for type of event and gender remained significant ($F(1, 1427) = 6.97$, $p = .008$, partial $\eta^2 = 0.005$). There was no interaction of gender with number of recent life events ($F(1, 1427) = 0.349$, $p = .56$, partial $\eta^2 = 0.000$). Next, to examine whether our results are specific for events that happened a long time ago, we repeated our main analysis for participants who experienced their index event in the last five years ($n = 715$; 213 men and 502 women; 279 A1 index events and 436 non-A1 index events). An ANOVA with the PSS-I total scores as dependent variable and type of event and gender as fixed factors showed a significant main effect for gender ($F(1, 711) = 4.24$, $p = .04$, partial $\eta^2 = 0.006$; higher PSS-I scores for women), but no main effect for event ($p = .11$), nor an interaction effect between type of event and gender ($p = .50$), even though men do show higher symptoms for life events than for A1 events. The finding that life events are at least as burdensome as A1 events holds up, but the finding that men report significantly more symptoms after non-A1 than A1 events is less clear for more recent events.

In the DSM-5 the A1 event 'sudden, unexpected death of someone close to you' was reformulated as 'sudden accidental death'. Additionally, the DSM-5 only qualifies sudden, catastrophic life-threatening illness or injury as an A1 event. Because the LEC was administered according to the DSM-IV-TR in the NESDA study, these details about the reported events are missing, hence we were unable to code all events according to the DSM-5. To check whether our results still hold when not including the A1 event categories from the LEC that would be modified according to the DSM-5 ('sudden, unexpected death of someone close to you' and 'life-threatening illness or injury'), we repeated our analyses leaving out all participants with an index event from one of these two A1 event categories ($n = 209$). An ANOVA with the PSS-I total score as dependent variable and type of event and gender as fixed factors shows that the interaction effect for type of event and gender

remained significant ($F(1, 1429) = 12.68$, $p < .001$, partial $\eta^2 = 0.009$), indicating that coding all index events according to the DSM-5 did not change our main findings.

A total of 99 individuals in the final dataset reported >1 index event. This group consisted of 24.2% men and 75.8% women, hence there are no gender differences compared to the rest of the sample ($\chi 2 = 1.57$, $p = .21$). We repeated our main analysis to check whether the results hold if these cases were omitted from the analysis. We performed an ANOVA with the PSS-I total score as dependent variable and type of event and gender as fixed factors. The main effects of gender ($p = .007$, partial $\eta^2 = 0.005$) and type of event ($p = .03$, partial $\eta^2 = 0.004$) as well as the interaction effect for type of event and gender remained significant ($p = .008$, partial $\eta^2 = 0.005$).

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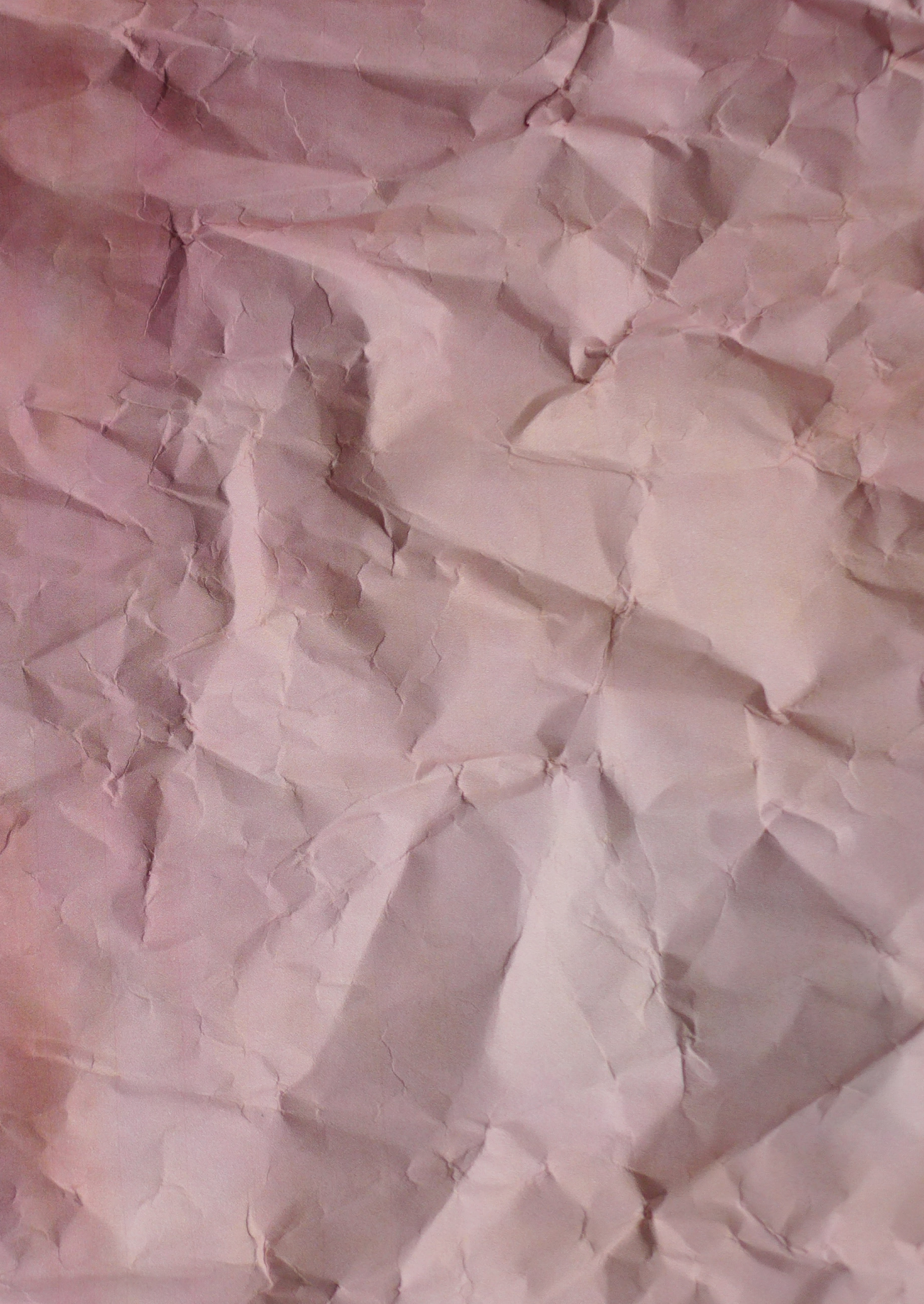
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Chapter 3

The role of hippocampal volume in the intergenerational transmission of child abuse and neglect - a multigenerational neuroimaging study

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ABSTRACT

Background. Experienced childhood maltreatment has repeatedly been associated with reduced hippocampal volume and enhanced stress reactivity in the hippocampus across the lifespan. The hippocampus also seems to be involved in normative parenting behavior. However, it is unknown whether hippocampal volume alterations are associated with maltreating parenting behavior as well and hence, whether it might play a role in the intergenerational transmission of child maltreatment.

Methods. The current multi-generational family study, including 180 participants with a wide age range (8-70 years) from two generations (parents and their offspring) of 53 families, is the first to investigate the role of hippocampal volume in the intergenerational transmission of child abuse and neglect.

Results. We found associations between experienced child abuse and reduced hippocampal volume, only in men. That is, men who experienced more abuse during their childhood showed smaller bilateral hippocampal volume than men who experienced less childhood abuse, with more pronounced effects in the right hippocampus. No associations between hippocampal volume and perpetrated abuse or neglect were found.

Conclusion. No indications were found for a mediating role of hippocampal volume in the intergenerational transmission of childhood abuse or neglect. Our study highlights the importance to distinguish between different subtypes of maltreatment in research and clinical practice and to take gender effects into account when investigating the impact of child maltreatment.

Key words: child maltreatment, child abuse, child neglect, intergenerational transmission, hippocampal volume, gender.

INTRODUCTION

Child maltreatment is a globally prevalent problem that impairs normative development in biological, social and psychological domains and is associated with serious life-long consequences (e.g., Heim, Shugart, Craighead, & Nemeroff, 2010; McCrory, De Brito, & Viding, 2011; Dannlowski et al., 2012). Some of these adverse consequences are associated with interpersonal functioning, including later parenting behavior (e.g., Norman et al., 2012). That is, parents who experienced maltreatment during childhood have an increased risk of maltreating their own children (e.g., Madigan et al., 2019; Van IJzendoorn, Bakermans-Kranenburg, Coughlan, & Reijman, 2020). However, to date few mechanisms explaining the maltreatment cycle within families have been adequately tested and/or confirmed (Alink, Cyr, & Madigan, 2019). To help identify risk factors for maltreating parenting behavior and design effective preventive interventions, revealing the mechanisms that might play a role in the intergenerational transmission of child maltreatment (ITCM) is crucial. The current multi-generational family study, including 180 participants with a wide age range (8-70 years) from two generations (parents and their offspring) of 53 families, is the first to investigate the role of hippocampal volume in the intergenerational transmission of child abuse and neglect.

Research shows that our brain is particularly sensitive to stress during (early) childhood, probably because of the important neural changes during this period (Lupien, McEwen, Gunnar, Heim, 2009). Early life stress (including childhood abuse and neglect) can have a number of structural and functional neurobiological consequences in key regions of the limbic system, in particular the hippocampus (e.g., Teicher et al., 2003), which have been associated with the onset and severity of psychopathology following child maltreatment (McCrory et al., 2011). The hippocampus is known as one of the most plastic and stress sensitive structures of the human brain and plays an important role in learning and memory (Teicher et al., 2003, 2018; McEwen, 2010; Dannlowski et al, 2012; Whittle et al., 2016). Various psychiatric disorders are associated with alterations in hippocampal volume (Geuze, Vermetten, & Bremner, 2005). Experienced childhood maltreatment has been associated with reduced hippocampal volume (e.g., Riem, Alink, Out, Van IJzendoorn, & Bakermans-Kranenburg, 2015; Whittle et al., 2016; Teicher et al., 2018), both in maltreated individuals with (Thomaes et al., 2010) and without psychopathology (e.g., Dannlowski et al., 2012). These reductions in hippocampal volume are more often reported in adults who experienced child maltreatment than in maltreated children and adolescents (Teicher & Samson, 2016; Whittle et al., 2016). This might suggest a silent period between exposure to maltreatment and its effect on neural development, also referred to as the “sleeper effect” of trauma (Briere, 1992). Possibly, early life stress and repeated adverse events cause a gradual loss of hippocampal synapses over time (Carrion, Weems, & Reiss, 2007). However, some longitudinal studies do suggest that alterations in hippocampal development can

already manifest just a few years after maltreatment experiences in children (e.g., Whittle et al., 2016) and may persist into adulthood, even in individuals without psychiatric disorders (Dannlowski et al., 2012). Hence, while there is evidence for an association between experienced child maltreatment and reduced hippocampal volume, findings regarding the exact mechanisms of this effect are mixed.

Furthermore, several other factors are important to take into account when examining the association between childhood maltreatment and hippocampal volume, such as laterality and gender. Findings regarding laterality are mixed. Some studies find effects only for the left or right hippocampus while other results show bilateral hippocampal volume alterations following maltreatment (for a review see Teicher & Samson, 2016). Gender is also an important factor, as the hippocampus seems to be more sensitive to stress in men than in women (e.g., Teicher & Samson, 2016; Whittle et al., 2016) even though the associations between PTSD and hippocampal volume seem to be driven by women (Logue et al., 2018). Mixed findings may be related to the potential protective effect of estrogen in women (McEwen, 2010). Estrogens modulate and mediate synapse and spine formation as well as neurogenesis in the hippocampus (Sheppard, Choleris, & Galea, 2019), and therefore stress may affect hippocampal development in men in particular (Teicher et al., 2018). Finally, type of maltreatment also seems important to take into account, 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; Teicher & Samson, 2016). Moreover, gender-specific effects of abuse versus neglect on hippocampal volume are also described as one of the most important gender differences in the developing human brain (Teicher et al., 2018).

Alterations in the neural substrates associated with exposure to childhood maltreatment, such as the hippocampus, are likely to play a key role in social functioning via its impact on emotion processing and responding (Elzinga & Bremner, 2002; Hart & Rubia, 2012) and the control of aggression (Davidson, Putnam, & Larson, 2000). Hence, disruptions in these neural substrates in parents who experienced childhood maltreatment might make them more vulnerable to maltreatment of their own children. We therefore hypothesize that the hippocampus might be involved in one of the mechanisms underlying ITCM. To date, in spite of evidence for an association between experienced child maltreatment and reduced hippocampal volume, research on the neural correlates of maltreating parenting behavior is scarce (Van IJzendoorn et al., 2020). While neurobiological antecedents are suggested to play an important role as parental risk factors in the aetiology of child maltreatment, there are major gaps in knowledge regarding those neural antecedents of maltreatment. Functional imaging studies have demonstrated the involvement of the hippocampus in normative parenting behavior (Swain, Lorberbaum, Kose, & Strathearn, 2007). Context and memory processing regions, neural arousal and salience detection centers including the hippocampus support adequate parenting behaviors. For example,

increased hippocampal activation was found while parents were exposed to the cry sounds of their own infant (Swain et al., 2004). Moreover, increased hippocampal activation was also found in mothers who were exposed to images of their own infant versus familiar and unknown infant facial images (Strathearn, 2002). However, to the best of our knowledge, little is known about the association between maltreating parenting behavior and hippocampal volume.

The current study is the first to examine the associations of (bilateral) hippocampal volume with both experienced childhood maltreatment and perpetrated maltreating behavior, enabling the investigation of the potential mediating role of hippocampal volume in ITCM. We used a multi-informant, multigenerational family design including 180 participants with a wide age range (8-70 years) from two generations of 53 families. We differentiated between effects of (experienced and perpetrated) abuse and neglect, as different types of maltreatment might be differentially associated with hippocampal volume (e.g., Hanson et al., 2015; Teicher & Samson, 2016). We also examined the role of gender and possible age effects on the association between hippocampal volume and experienced childhood maltreatment. We hypothesized that experienced childhood abuse and neglect are associated with reduced hippocampal volume, and that these effects are more pronounced in older participants who experienced child abuse. We also predicted to find a stronger association between experienced maltreatment and reduced hippocampal volume in men than in women. Furthermore, we hypothesized that reduced hippocampal volume is associated with perpetrated childhood maltreatment as well, and we examined whether hippocampal volume (partly) mediates ITCM.

METHOD

Participants

The current sample is a subsample from the larger 3 Generation (3G) parenting study, a three-generation family study on the intergenerational transmission of parenting styles, stress and emotion regulation (see also Van den Berg et al., 2018; Van den Berg, Tollenaar, Compier-de Block, Bakermans-Kranenburg, & Elzinga, 2019; Buisman et al., 2020). For this family study, participants were recruited via three other studies that included the assessment of caregiving experiences (Penninx et al., 2008; Scherpenzeel, 2011; Joosen, Mesman, Bakermans-Kranenburg, & Van IJzendoorn, 2013). Participants with an increased risk of experienced maltreatment were oversampled. Participants who had at least one child of 8 years or older were invited to participate in the 3G study. After their consent, their family members (parents, partners, offspring, adult siblings, nephews, nieces and in-laws) were invited to participate as well (total n = 395). All participants from the 3G study who participated in the fMRI part of the study were included for the current study. In

total, we included 180 participants (*n* = 78 men and *n* = 102 women) from two generations (parents and their offspring) of 53 families. The mean age of the parents (*n* = 101; 45 men and 56 women) was 46.9 years (SD = 10.67, age range: 26.6-69.7 years) and the mean age of the offspring (*n* = 79; 33 male and 46 female) was 18.6 (SD = 7.75, age range: 8.0-40.1 years). See Supplement for more information on the relatedness, ethnicity and educational level of our participant sample.

Procedure

Written informed consent was obtained from all participants. We invited participants and their families to our lab at the Leiden University Medical Center (LUMC) for one or two days, depending on family composition. Participants with children visited the lab once with their family of origin and once with their nuclear family. During these laboratory visits, questionnaires and computer tasks were completed and saliva and hair samples were collected. Furthermore, participants did several interaction tasks together with their family members. If eligible, parents and their offspring were asked to participate in the MRI part of the 3G study. Imaging included several structural and functional scans. Results regarding the functional scans are reported elsewhere (Van den Berg et al., 2018, 2019). All offspring younger than 18 years were first familiarized with the MRI scanner using a mock scanner. The full protocol was conducted according to the principles expressed in the Declaration of Helsinki and approved by the Medical Ethics Committee of the LUMC (P11.134).

Measures

Childhood maltreatment

Experienced childhood abuse and neglect, perpetrated by mother and/or father, were assessed in all participants using adapted versions of the Conflict Tactics Scales (CTS; Straus, Hamby, Finkelhor, Moore, & Runyan, 1998) for emotional and physical abuse and physical neglect, which was supplemented with the emotional neglect scale from the Childhood Trauma Questionnaire (CTQ-SF; Bernstein et al., 2003; see also Buisman et al., 2020). All parents also filled out a CTS version in which they reported on their own perpetrated abusive and/or neglectful behaviors towards (each of) their child(ren). For experienced and perpetrated maltreatment separately, an overall Abuse score was comprised by averaging Emotional and Physical Abuse, and an overall Neglect score by averaging Emotional and Physical Neglect. Whenever possible, we combined information from multiple informants: offspring (experienced childhood maltreatment) and their parents (perpetrated child maltreatment; see Supplement). Because the distribution of the CTS data was skewed, scores were log-transformed (log10). Outliers (values more extreme than a standardized value of +/- 3.29), were winsorized to the most extreme value within the normal range plus

or minus the difference between the two most extreme values within the normal range (*n* = 1 for experienced abuse and *n* = 1 for experienced neglect; Tabachnik & Fidell, 2001).

Covariates

Demographic information (age, gender, handedness and household social economic status (SES)) was assessed for all participants using questionnaires. Psychopathology symptoms were assessed based on three versions of Achenbach's screening questionnaires. For children younger than 12 years old, parents completed the Child Behavioral Checklist (CBCL; Achenbach, 1991). Participants aged 12-17 years filled out the Youth Self Report (YSR; Achenbach & Rescorla, 2001) and for participants from 17 years up the Adult Self Report (ASR; Achenbach & Rescorla, 2003) was used. A total psychopathology symptom score was calculated per questionnaire. Cronbach's alphas were good to excellent (.83-.97). To control for total intracranial volume (ICV), ICV was added as a covariate as well (see subsection 2.5 for more information on the MRI data analysis).

MRI data acquisition

High-resolution T1-weighted scans were acquired for all participants using a standard whole-head coil on a 3-T Philips Achieva scanner (Philips Medical Systems, Best, The Netherlands) in the LUMC. Foam inserts that surrounded the head were used to minimize head movement. Scan parameters were as follows: TR = 9.8 ms, TE = 4.6 ms, flip angle = 8°, 140 slices, voxel size = 0.875 x 0.875 x1.2 mm, FOV = 224×177×168 mm. All anatomical MRI scans were inspected by a neuroradiologist from the Radiology department of the LUMC. No anomalous findings were reported.

MRI data analysis

Cortical reconstruction and volumetric segmentation was performed using standard procedures in the FreeSurfer software (version 5.3.0), which is freely available (http://surfer.nmr.mgh.harvard.edu/). See Supplement for a short description of this process.

Subcortical segmentations of the hippocampus were visually inspected for accuracy according to standardized protocols designed to facilitate harmonized image analysis across multiple sites (http://enigma.ini.usc.edu/protocols/imaging-protocols/; see also e.g., Bas-Hoogendam et al., 2018). This quality control resulted in the exclusion of four participants. In addition, data of four other participants were excluded because the brain could not be reliably reconstructed from the T1-weighted scans using FreeSurfer. Volumes of the right and left hippocampi were checked for outliers (i.e., values with a standardized value of +/- 3.29) and winsorized when necessary (*n* = 1). Volumes of the left and right hippocampus (mm3) and total ICV (mm3) were included in the statistical analyses in SPSS (see below).

Multilevel analyses

Using SPSS 23, we employed three-level multilevel regression analyses to take the family structure of the data into account to examine whether experienced and perpetrated maltreatment was associated with hippocampal volume. Participants were nested within households (i.e., parents with their offspring) and households were nested within families (i.e., related households). Therefore, a model with three levels was specified, in which level 1 estimates variation at the participant level, level 2 captures variation among participants within the same households and level 3 models variation among families. Random intercept models were built sequentially. To test for random variation in the outcome variables at the different levels and compute the intraclass correlation coefficients (ICC) at the family and household level, we started with an empty (null) model without explanatory variables (see Table 1). Independent of ICC, multilevel analyses were consistently used to match the hierarchical structure of our data.

Table 1. Variance accounted for (ICCs) on household and family level.

	Hippocampus (bilateral)	Hippocampus (right)	Hippocampus (left)
Family level	.265	.241	.264
Household level	.002	.004	.012

Next, age, gender, handedness, ICV, socio-economic status (SES) and psychopathology were entered to the model as possible covariates. Because of the large age range in our study and because early adverse experience may yield different neurobiological manifestations in men and women (Teicher et al., 2003), age and gender were always included as covariates and factors in the final model. All other covariates were omitted when *p*-values exceeded .05. Separate models were run for experienced maltreatment (all participants: n = 180) and perpetrated maltreatment (parents only: n = 101). In Model 1 the main effects of abuse and neglect were added to examine the fixed effects of abuse and neglect. For experienced maltreatment a second model was tested in which the interaction effects of age x abuse, gender x abuse, age x neglect and gender x neglect were added. For the first multilevel regression analyses right- and left hippocampal volumes were combined. In case of significant results for bilateral hippocampal volume, we repeated our analyses for right- and left hippocampal volumes separately to examine possible effects of lateralization. All (continuous) predictor variables and covariates were centered. All independent and dependent variables were measured at the individual level (except SES, which was measured at the level of the household) and considered in the fixed part of the model. If both experienced and perpetrated maltreatment were found to be associated with hippocampal volume, mediation analyses were planned to examine the role of hippocampal volume in ITCM. However, this was not the case for the findings of this study.

RESULTS

Intergenerational transmission of childhood maltreatment

Characteristics of the sample (including maltreatment scores) are summarized in Table 2. Experienced abuse and neglect were strongly associated (r = .52, p < .001), and parental abusive and neglectful behavior were moderately associated (r = .38, p < .001). For all participants with offspring (n = 101 parents) regression analyses were conducted with experienced abuse and neglect as predictors and abusive and neglectful behavior as outcome measures separately to examine intergenerational transmission of childhood abuse and neglect in the current sample. Standardized regression coefficients are reported. Controlling for age, gender, household SES and psychopathology in the first block, experienced abuse (β = .50, t(94) = 4.68, p < .001) was a significant predictor of abusive behavior, whereas experienced neglect did not predict abusive behavior (β = -.14, t(94) = -1.24, p = .217) and none of the covariates were significant. Experienced neglect (β = .02, t(94) = 0.13, p = .897) and experienced abuse (β = -.04, t(94) = -0.32, p = .749) did not predict neglectful behavior. Psychopathology (β = .30, t(94) = 2.88, p = .005) was the only significant covariate for neglectful behavior.

Table 2. Demographics and maltreatment scores (full sample n = 180).

Variables	Mean (SD)	Range
Age	34.50 (17.00)	8.00 - 69.67
Gender (*n:* men/women)	78/102	-
Handedness (*n*: left/right)	23/157	-
Abused[a]	1.62 (0.48)	1.00 - 4.50
Neglected[a]	1.83 (0.57)	1.00 - 5.00
Maltreated[a] (total)	1.73 (0.47)	1.02 - 4.75
Abusive[b] (n = 101)	1.46 (0.31)	1.00 - 2.53
Neglectful[b] (n = 101)	1.58 (0.33)	1.00 - 2.48
Maltreating[b] (total; n = 101)	1.52 (0.26)	1.00 - 2.22

[a]Combined experienced maltreatment scores by averaging parent and child reports as measured with the CTS. [b]Combined maltreating behavior scores by averaging parent and child reports as measured with the CTS.
Values of all included participants are presented (n = 180) unless otherwise specified.
Raw scores are presented.

Multilevel analyses: hippocampal volume and maltreatment

The ICC was .265 at the family level and .002 at the household level for bilateral hippocampal volume (see Table 1), indicating that hippocampal volumes within families (but not within households) are more similar compared to unrelated participants. Since right and left hippocampal volumes were significantly correlated (r = .72, p < .001), multilevel

regression analyses were run using bilateral hippocampal volume to examine the associations with severity of experienced maltreatment (all participants: *n* = 180) and severity of perpetrated maltreating parenting behavior (participants with offspring: *n* = 101) separately. Only in case of significant findings, we repeated our analyses for right- and left hippocampal volumes separately. All multilevel regression analyses were run controlling for age, gender, handedness, ICV, SES and psychopathology. Unstandardized regression coefficients are reported.

Table 3. Multilevel models of hippocampal volume as related to experienced childhood abuse and neglect (*n* = 180).

Hippocampal volume									
	Bilateral			Right			Left		
	b	SE	*p*	*b*	SE	*p*	*b*	SE	*p*
Null model									
age	-13.93	3.83	.000**	-6.50	2.02	.002**	-8.05	2.35	.001**
gender (0=men)	591.69	124.58	.000**	284.33	66.14	.000**	315.01	76.84	.000**
handedness	256.83	195.05	.190	147.79	103.03	.153	141.39	119.77	.239
ICV	< 0.01	< 0.01	.209	< 0.01	< 0.01	.061	< 0.01	< 0.01	.459
SES	136.02	106.89	.205	37.15	55.32	.503	107.14	64.52	.099
PP	-445.94	328.16	.176	-117.14	172.86	.499	-352.61	201.11	.081
Model 1									
abused	-1269.33	732.47	.085	-633.22	383.86	.101	-606.54	450.20	.180
neglected	937.12	695.45	.180	569.92	366.14	.121	390.72	428.92	.364
	χ^2 (2) = 3.41		.182	χ^2 (2) = 3.57		.168	χ^2 (2) = 1.91		.385
Model 2									
abused*age	35.14	40.10	.382	15.73	21.15	.458	24.11	24.93	.335
neglected*age	-58.52	37.61	.122	-33.65	19.85	.092	-23.88	23.37	.308
	χ^2 (2) = 2.41		.300	χ^2 (2) = 2.79		.248	χ^2 (2) = 1.36		.506
Model 3									
abused*gender	-3091.66	1376.48	.026*	-1809.55	724.62	.013*	-261.36	861.69	.145
neglected*gender	118.93	1253.32	.925	97.89	660.99	.882	-43.79	785.53	.956
	χ^2 (2) = 6.64		.036*	χ^2 (2) = 8.03		.018*	χ^2 (2) = 3.08		.214

* $p < .05$; ** $p < .01$
ICV = intracranial volume; SES = social economic status; PP = psychopathology

Hippocampal volume: associations with experienced abuse and neglect

Results for the multilevel analyses with experienced abuse and neglect as predictors and bilateral hippocampal volume as outcome measure are shown in Table 3. Age (β = -13.93, SE = 3.83, $p < .001$; with smaller hippocampal volume in older participants) and gender (β = 591.69, SE = 124.58, $p < .001$; larger hippocampal volume in men compared to women)

were the only significant covariates. In contrast to our expectations, no significant main effects were found for experienced abuse or neglect, nor significant interaction effects with age, on bilateral hippocampal volume (all $p > .08$). Results also showed no significant interaction between experienced neglect and gender on bilateral hippocampal volume ($\beta = 118.93$, SE = 1253.32, $t = 0.10$, $p = .925$). However, results did reveal a significant improvement of the model when the interaction between abuse and gender was added to the model (χ^2 (2) = 6.64, $p = .036$). The interaction term ($\beta = -3091.66$, SE = 1376.48, $t = -2.25$, $p = .026$) indicates that in men who experienced more childhood abuse bilateral hippocampal volumes were smaller than men who experienced less abuse, while for women bilateral hippocampal volume was not related to experienced abuse (see Figure 1).

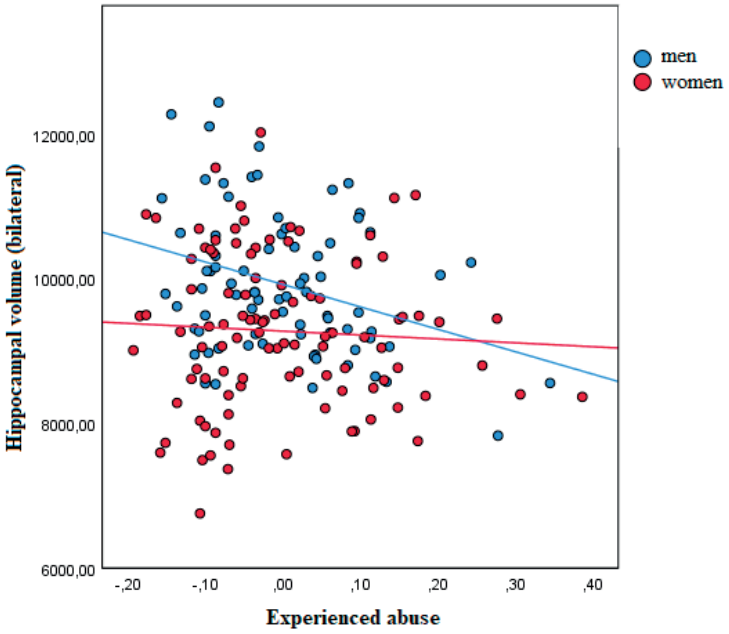


Figure 1. Visual representation of the significant interaction effect between experienced abuse and gender for bilateral hippocampal volume.

Additionally, we performed exploratory post-hoc analyses for right and left hippocampal volumes separately to examine possible lateralization effects (see Table 3). In the right hippocampus the same interaction effect between abuse and gender was found following the same interaction pattern ($\beta = -1809.55$, SE = 724.62, $t = -2.497$, $p = .013$) as was found for bilateral hippocampal volume. This was not the case for the left hippocampus ($\beta = -1261.36$, SE = 861.69, $t = -1.464$, $p = .145$).

Hippocampal volume: associations with abusive and neglectful behavior

Multilevel analyses were conducted for participants with offspring (n = 101) with abusive and neglectful behavior as predictors and bilateral hippocampal volume as outcome measure. Gender (p < .001) was again a significant covariate showing larger bilateral hippocampal volume in men compared to women, whereas age was not a significant covariate among participants with offspring. Results showed no significant main effects for abusive (p = .836) or neglectful behavior (p = .704) for bilateral hippocampal volume (see Table 4). Consequently, no mediation analyses on ITCM were conducted.

Table 4. Multilevel models of hippocampal volume as related to abusive and neglectful behavior (n = 101).

Bilateral hippocampal volume			
	b	SE	*p*
Null model			
age	-12.84	8.83	.149
gender	611.15	167.60	.001**
handedness	92.96	293.93	.753
ICV	< -0.01	< 0.01	.528
SES	209.72	139.49	.137
PP	-718.77	445.34	.110
Model 1			
abusive	-239.14	1155.66	.836
neglectful	-445.79	1170.51	.704
	χ^2 (2) = 0.28		.869

* p < .05; ** p < .01

ICV = intracranial volume; SES = social economic status; PP = psychopathology

DISCUSSION

The primary aim of the current study was to examine the potential role of hippocampal volume in ITCM using a multigenerational family study design. This design enabled us to differentiate between effects of (experienced and perpetrated) abuse and neglect. Moreover, we examined age and gender effects on the association between hippocampal volume and experienced childhood maltreatment.

Experienced abuse and neglect

Against our hypotheses, we found no associations between experienced childhood abuse or neglect and hippocampal volume in our total sample of participants. This is not in line with previous studies reporting reductions in hippocampal volume in maltreated individu-

als (e.g., Riem et al., 2015; Whittle et al., 2016; Teicher et al., 2018). However, we did find an interesting gender effect in this respect. Previous findings on gender differences in hippocampal volume have not always been consistent, which might be (partly) due to the use of different types of analyses or sample sizes (Perlaki et al., 2014). Our findings indicate that men who experienced more abuse during their childhood show smaller bilateral hippocampal volume than men who experienced less childhood abuse. These effects are particularly present in the right hippocampus. For women, experienced abuse or neglect were not related to hippocampal volume. This is in line with previous research showing that the male hippocampus is more sensitive to stress than the female hippocampus (e.g., Teicher & Samson, 2016; Whittle et al., 2016). Gender differences in the effects of experienced maltreatment on hippocampal volume may result in different neurocognitive and neuropsychological consequences (Teicher et al., 2018). These gender differences may be due to the potential protective effect of estrogen in women (McEwen, 2010) and dimorphic differences in developmental trajectory (Teicher et al., 2018). Childhood stress may affect hippocampal development in women by enhancing pubertal pruning, while it may lead to decreasing neurogenesis in men.

The finding that hippocampal volume in men was only associated with experienced abuse and not with experienced neglect is consistent with studies showing that specific types of maltreatment seem to selectively affect sensory systems and neural pathways that process stressful and traumatic incidents (Teicher & Samson, 2016). Our findings regarding the association between hippocampal volume and experienced abuse are consistent with previous studies showing reduced hippocampal volume to be more strongly associated with experienced childhood abuse than with experienced childhood neglect (e.g., Hanson et al., 2015; Teicher & Samson, 2016). However, those previous studies report their findings mostly in abused adults, whereas the current study demonstrates reduced hippocampal volume in abused men with a large age range.

Atypical hippocampal volume as a result of experienced child maltreatment might manifest as hippocampal asymmetry. Mixed findings regarding laterality in the literature are partly related to differences in sample characteristics such as age (Teicher & Samson, 2016). For example, greater right-sided than left-sided hippocampal effects are reported in adults with borderline personality disorder or without psychopathology. This highlights the importance of including participants with a large age range. In the current study a sample with a wide age range (8.0 to 69.7 years) was included which may help clarify the inconsistent findings regarding hippocampal volume in maltreated children and adolescents compared to adults (e.g., Edmiston et al., 2011). Since reductions in hippocampal volume are more often found in adults maltreated as children than in maltreated children and adolescents (Teicher & Samson, 2016; Whittle et al., 2016) we expected to find more pronounced effects of experienced maltreatment in older participants. In general, irrespective of maltreatment, we found smaller bilateral hippocampal volume in older partici-

pants in the current sample, even though in the older subsample of parents, age was not a significant predictor. This is in line with other studies showing loss of hippocampal volume into adulthood in the general population (e.g., Erickson et al., 2010). While estimates of age-related hippocampal volume loss vary widely across different studies, almost all report negative correlations between age and hippocampal volume (for a review see Van Petten, 2004). Importantly though, no interaction effects between experienced maltreatment and age were found in the current study. A within subject longitudinal design might further examine any age effects of the impact of experienced maltreatment, but our results suggest that the effect on hippocampal volume in men may be independent of age at measurement of the hippocampal volume.

Abusive and neglectful behavior

Even though some (functional) MRI studies have demonstrated the involvement of the hippocampus in parenting behavior in general (Swain et al., 2007), to date little is known about the role of hippocampal volume in maltreating parenting behavior. To the best of our knowledge the current study is the first to examine the association between abusive and neglectful behavior and hippocampal volume using a large multigenerational sample. Reduced hippocampal volume might play a role in the intergenerational transmission of maltreatment, because it has been associated with dysregulated responses to stress (Riem et al., 2015). Our findings provide indications that parental abusive or neglectful behavior is not associated with hippocampal volume. While alterations in specific regions of the human brain (including the hippocampus) following experienced childhood maltreatment have been consistently found across populations, linking such brain changes to brain function and future behavior seems to be more complex (e.g., Van den Berg, 2018, 2019). Even when it comes to memory, one of the most well-known functions of the hippocampus, mixed findings are reported regarding the size-function relationship of the hippocampus (e.g., Pohlack et al., 2014). For example, some studies report a surprisingly weak association between hippocampal size and episodic memory ability (e.g., Van Petten, 2004; Charlton, Barrick, Markus, & Morris, 2010). More research is needed to further understand the neural correlates of maltreating parenting behavior. An alternative explanation for our findings could be that the role of hippocampal volume in maltreating parents with a history of maltreatment is masked by compensatory changes in other brain regions (e.g., Van der Werff, Van den Berg, Pannekoek, Elzinga, & Van der Wee, 2013; Galinowski et al., 2015). This highlights the importance to also include other brain areas and their connectivity that might play a role in parenting behavior in future research, for example the corpus callosum, the anterior cingulate and the dorsolateral prefrontal cortex.

Intergenerational transmission of maltreatment

While we found smaller bilateral hippocampal volume in men who experienced more childhood abuse, parental abusive behavior was not associated with hippocampal volume. Hence, no indications were found for a role of hippocampal volume in ITCM in the current study.

On a behavioral level we observed intergenerational transmission of abuse, whereas intergenerational transmission of neglect was not found. This is in line with our findings regarding transmission of maltreatment in the total sample (n = 395) of the 3G Parenting study, where intergenerational transmission of abuse was consistently found independent of the informant (Buisman et al., 2020). The transmission of neglect was only found when analyses were based on the perspective of a single reporter. That is, self-reported experienced neglect predicted self-reported perpetrated neglect, but intergenerational transmission of neglect was not found using the current multi-informant approach where reports of different informants from each generation were combined. This calls the validity of the intergenerational transmission of neglect into question.

Limitations and recommendations for future studies

It is important to note that the majority of our participants reported about child maltreatment retrospectively. On the one hand, research shows that retrospective reports of maltreatment may be verifiable (Chu, Frey, Ganzel, & Matthews, 1999). On the other hand, a recent meta-analysis reports poor agreement between prospective and retrospective measures of childhood maltreatment (Baldwin, Reuben, Newbury, & Danese, 2019). Recall bias might have affected reports of childhood events in our study. A prospective study following three generations would be recommended, but practical possibilities to conduct such a study may be limited.

A few other limitations should also be taken into account when drawing conclusions based on our findings. Since not all participants were parents, we had less statistical power to examine the effects of perpetrated maltreatment than the effects of experienced maltreatment. Hence, the fact that we only found associations for experienced abuse and neglect and not for abusive and neglectful behavior may (partly) be due to differences in sample size. Another limitation of the current study is the lack of exact information on the age of exposure to the maltreatment experiences, although maltreatment tends to be chronic for many children (e.g., Gilbert et al., 2009). Future research should take this timing into account to examine possible sensitive exposure periods on hippocampal volume which might also be gender-specific (Teicher et al., 2018). Moreover, replication studies are warranted to determine the empirical robustness of our findings.

Conclusion

Our study highlights the importance to distinguish between different types of maltreatment and to take gender effects into account when investigating the associations between abuse and neglect and hippocampal volume. We found associations between experienced child abuse and reduced hippocampal volume in men. That is, men who experienced more abuse during their childhood show smaller bilateral hippocampal volume than men who experienced less childhood abuse, with more pronounced effects in the right hippocampus. No associations between hippocampal volume and perpetrated maltreatment (abuse or neglect) were found. Hence, we found no indications for a mediating role of hippocampal volume in ITCM.

The hippocampus is one of the most sensitive and plastic regions of the brain (McEwen, 2010). This plasticity might be functional to protect against permanent neural damage, but at the same time it may increase its vulnerability to stress. All the same, volume loss of the hippocampus as a result of childhood maltreatment points towards the need to examine effects of efforts to alleviate hippocampal volume reduction through psychotherapeutic or psychopharmacological interventions. For example, promising preliminary results show that mindfulness is associated with increased hippocampal volume and with improvement in hippocampal-dependent cognitive performance in maltreated young adults (Teicher & Samson, 2016). Further research into other neural mechanisms that might play a role in the intergenerational transmission of abuse and neglect is important for the design and implementation of effective preventive interventions.

CONFLICT OF INTEREST

None declared.

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SUPPLEMENT

Participants

The total sample of participants for the current study included six parent-child pairs with two parents and two children (n = 24), 13 pairs with two parents and one child (n = 39), 13 pairs with one parent and two children (n = 39), 17 pairs with one parent and one child (n = 34) and one pair with two children and three parents (two biological parents and a stepfather; n = 5). Additionally, 29 parents participated without their children and 10 children participated without their parents participating. The vast majority of all participants (96%) were Caucasian, five participants were of Latin-American descent and two of mixed descent. Elementary school or a short track of secondary school was completed by 27% of all participants, 33% held an advanced secondary school or vocational school diploma, 18% held a college or university degree and 7% a postgraduate diploma. 10% of all participants were still in elementary school. Education level of 5% was unknown, but most of these participants were under 17 years old.

Childhood maltreatment

For 123 out of 180 participants at least two informants (offspring and their parents) reported on maltreatment from the experienced and perpetrator perspective, respectively. In a similar vein, for 83 out of 101 parents at least two informants (parents and their children) reported on maltreating behavior.

MRI data analysis

The technical details of these procedures are described elsewhere (e.g., Fischl & Dale, 2000; Fischl et al., 2004a, 2004b; Jovicich et al., 2006; Reuter, Rosas, & Fischl, 2010). In short, this process includes motion correction, removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Ségonne et al., 2004), automated Talairach transformation, segmentation of subcortical volumetric structures (Fischl et al., 2002; Fischl et al., 2004a), intensity normalization (Sled, Zijdenbos, & Evans, 1998), tessellation of the gray matter white matter boundary, automated topology correction (Fischl, Liu, & Dale, 2001; Ségonne, Pacheco, & Fischl, 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale & Sereno, 1993; Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000). Separate volumes of the right and left hippocampi (mm3) were generated for each participant. Additionally, total individual ICV (mm3) was extracted to use as a covariate in our analyses. Freesurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths (Han et al., 2006; Reuter, Schmansky, Rosas, & Fischl, 2012).

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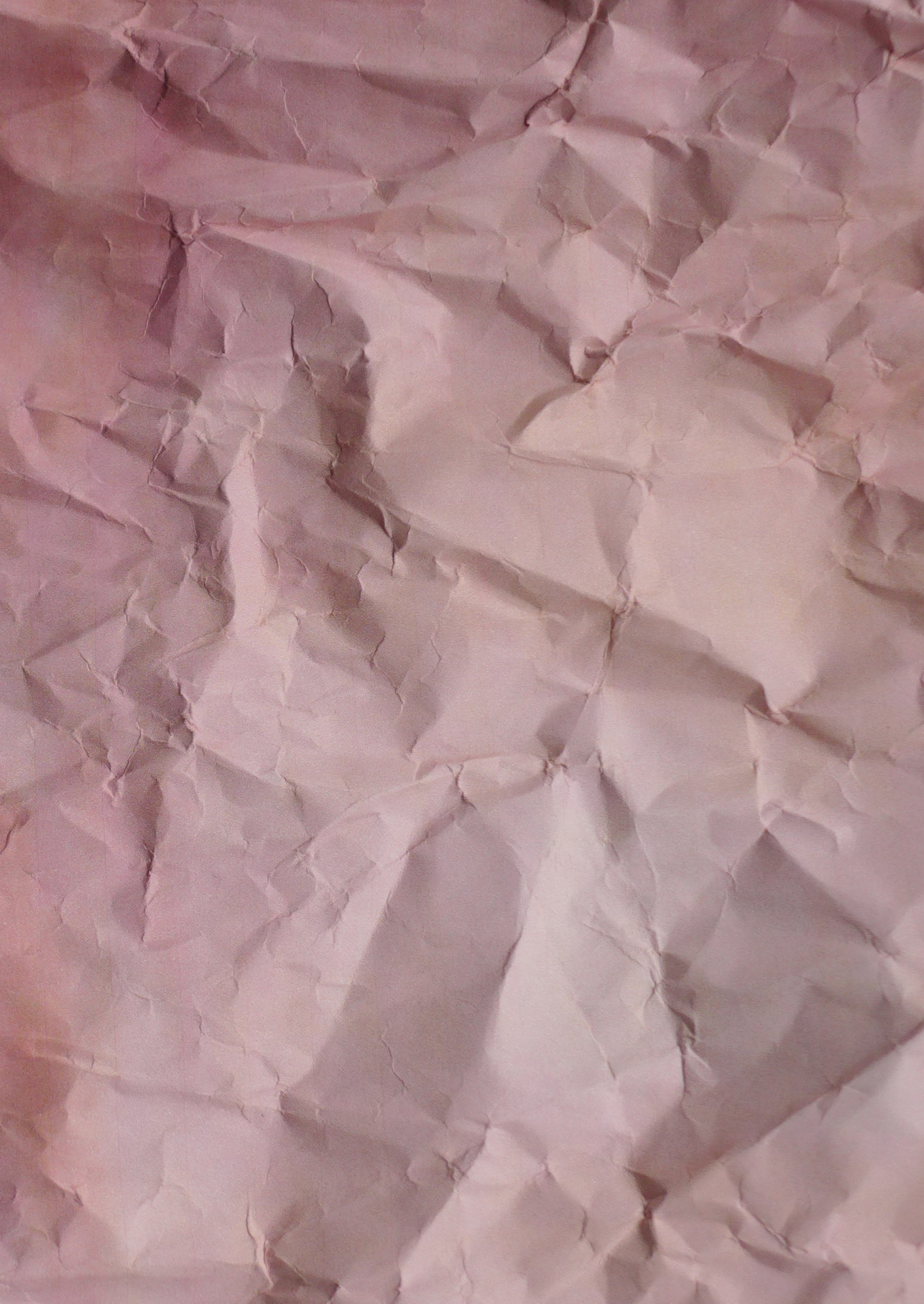
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Chapter 4

An intergenerational family study on the impact of experienced and perpetrated child maltreatment on neural face processing

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ABSTRACT

Background. Altered processing of emotional faces due to childhood maltreatment has repeatedly been reported, and may be a key process underlying the intergenerational transmission of maltreatment.

Methods. The current study is the first to examine the role of neural reactivity to emotional and neutral faces in the transmission of maltreatment, using a multi-generational family design including 171 participants of 51 families of two generations with a large age range (8–69 years). The impact of experienced and perpetrated maltreatment (abuse and neglect) on face processing was examined in association with activation in the amygdala, hippocampus, inferior frontal gyrus (IFG) and insula in response to angry, fearful, happy and neutral faces.

Results. Results showed enhanced bilateral amygdala activation in response to fearful faces in older neglected individuals, whereas reduced amygdala activation was found in response to these faces in younger neglected individuals. Furthermore, while experienced abuse was associated with lower IFG activation in younger individuals, experience of neglect was associated with higher IFG activation in this age group, pointing to potentially differential effects of abuse and neglect and significant age effects. Perpetrated abusive and neglectful behavior were not related to neural activation in any of these regions.

Conclusion. No indications for a role of neural reactivity to emotional faces in the intergenerational transmission of maltreatment were found.

Keywords: Child maltreatment; Emotional face processing; Amygdala; Hippocampus; IFG; Insula

INTRODUCTION

Exposure to childhood maltreatment (i.e. 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., 2011a; Norman et al., 2012). One of the striking consequences of experienced childhood maltreatment is the increased risk for maltreating own offspring. Around 30% of maltreated individuals maltreat their own children, a percentage that is significantly lower in non-maltreated individuals (e.g., Dixon et al., 2005; Berlin et al., 2011). Unravelling the mechanisms behind this intergenerational transmission of childhood maltreatment is crucial for the design of effective preventive interventions. Our study, using a multi-informant, multi-generational family design including 171 participants with a wide age range (8–69 years), is the first to examine directly the role of neural reactivity to emotional faces in the intergenerational transmission of abuse and neglect within two generations of families. Changes in emotional face processing due to maltreatment are characterized by hypervigilance to (negative) emotional facial cues. For example, maltreated children exhibited selective attention to angry faces (Pollak and Tolley-Schell, 2003). Physically abused children were found to be hypervigilant to hostile cues (Dodge et al., 1995) and needed less visual information to accurately identify facial displays of anger (e.g., Pollak and Sinha, 2002). On the other hand, maltreated children were less accurate in recognizing positive emotional states of others (Koizumi and Takagishi, 2014). Attentional and interpretation biases have also been found in older maltreated individuals. For example, abused young adults displayed preferential attention to angry faces and increased sensitivity in the detection of angry facial expressions (Gibb et al., 2009). From an evolutionary perspective it is useful to process facial expressions rapidly when growing up in a maltreating environment, because they can provide signs of either threat or safety. However, in the course of time enhanced reactivity to negative emotional faces may put maltreated individuals at increased risk to develop a persistent vigilance for threat-related facial expressions and an attentional bias towards threatening or negative information in general, which is often associated with psychopathology such as anxiety and depressive disorders (e.g., Gibb et al., 2009). From a parenting perspective, infant facial cues are crucial to elicit nurturing behaviors from parents. Deficits in recognizing and responding to these emotional face cues may therefore affect parenting behavior. Indeed, deficits in emotional face processing were found to be associated with parental insensitivity (e.g., Thompson-Booth et al., 2014). Also, parents at high risk for physical child abuse made more errors in recognizing pictures of emotional faces (Asla et al., 2011). This puts one of the possible consequences of experienced childhood maltreatment, i.e., deviances in emotional face processing, on the list of possible risk factors for parental maltreating behavior, and hence this may be a possible mediator in the transmission of maltreatment (e.g., Asla et al., 2011; Wagner et al., 2015). Altered emotional face processing following

experienced childhood maltreatment may be reflected in chronic functional alterations in the brain. The amygdala plays a central role in the processing of emotional faces (e.g., Davis and Whalen, 2001). In line with enhanced sensitivity to facial expressions, adults with a history of childhood (emotional) maltreatment showed enhanced bilateral amygdala reactivity to neutral and emotional faces (McCrory et al., 2011b; Dannlowski et al., 2012; Van Harmelen et al., 2013). Differential neural processing of facial stimuli in maltreated individuals has also been observed in other brain areas, particularly the hippocampus and insula. Maltreated children for example showed increased reactivity in the left anterior insula in response to angry faces (McCrory et al., 2011b), and neglected youths displayed significantly higher activation in the left amygdala and left anterior hippocampus while viewing angry and fearful faces (Maheu et al., 2010). In adults, experienced childhood maltreatment has been associated with higher activity in face processing areas (fusiform gyri and left hippocampus) while novel compared to familiar adult faces were presented (Edmiston and Blackford, 2013). The IFG is also considered as one of the core regions of emotional face processing (e.g., Haxby et al., 2002; Sabatinelli et al., 2011). Several studies show that IFG activation is associated with expressive face processing (e.g., Carr et al., 2003; Fusar-Poli et al., 2009). Moreover, physically maltreated adolescents showed higher IFG activation while fearful faces were presented compared to healthy controls (Hart et al., 2018). However, whether the impact of childhood maltreatment on neural responsivity in these brain areas is also associated with caregiving behavior in adulthood is still unknown. The neural alterations following child maltreatment span across brain regions (including the amygdala, hippocampus, insula and IFG) that are also involved in caregiving behavior (DeGregorio, 2013; Rilling and Mascaro, 2017; Swain and Ho, 2017). Of note, intrusive mothers exhibited higher activation in the right amygdala while watching videos of their own versus an unfamiliar child (Atzil et al., 2011), and greater activation to their own infant's cry in the left anterior insula and temporal pole (Musser et al., 2012). However, research on the neural correlates of maltreating parenting behavior is scarce, and the current study is the first to examine whether altered neural reactivity to emotional faces is involved in the intergenerational transmission of child maltreatment using a family design. Furthermore, as different types of maltreatment, i.e., abuse and neglect, may have specific effects on emotion processing and recognition (Compier-de Block, 2017; Van den Berg et al., 2018), our study design also allows for a differentiation of effects of (experienced and perpetrated) abuse and neglect. To investigate intergenerational transmission of maltreatment in our sample, we investigated whether maltreated individuals were more likely to show maltreating behavior towards their children. To examine whether alterations in neural reactivity to emotional faces in the amygdala, hippocampus, IFG and insula are involved in the intergenerational transmission of abuse and neglect we investigated whether a history of abuse and/or neglect was associated with altered brain reactivity in response to emotional and neutral faces in these areas. Next, we investigated whether abusive and

neglectful behavior was associated with altered activation in these same brain regions. Furthermore, we examined whether abuse and neglect showed differential effects. Lastly, given the large age range in our sample, we investigated whether age moderated associations between neural reactivity to emotional and neutral faces and experienced and perpetrated maltreatment.

METHOD

Participants

Participants in the current study were part of a larger sample from the 3G parenting study, a family study on the intergenerational transmission of parenting styles, stress and emotion regulation (see also Compier-de Block, 2017; Van den Berg et al., 2018). The current sample was recruited via three other studies that included instruments to assess caregiving experiences (Penninx et al., 2008; Scherpenzeel, 2011; Joosen et al., 2013). From two of these studies we recruited only participants who reported that they had experienced some form of childhood maltreatment. All participants from the third study were recruited. Thus, participants with an increased risk of experienced maltreatment were oversampled. Only those participants who indicated to be willing to participate in other research, and with at least one child of 8 years or older were approached. After their consent for participation, we invited their family members (parents, partners, offspring, adult siblings, nephews, nieces and in-laws) to participate. For the current study, all participants from the 3G study who participated in the functional magnetic resonance imaging (fMRI) part were included. In total, we included 171 participants (n = 73 men and n = 98 women) from two generations (parents and their offspring) of 51 families. The mean age of the parents (n = 100; 45 men and 55 women) was 46.6 years (SD = 10.72, age range: 26.6–69.7 years) and the mean age of the offspring (n = 71; 28 male and 43 female) was 19.0 (SD = 7.32, age range: 8.3–37.0 years). See Supplement for more information on the relatedness, ethnicity and educational level of our participant sample.

Procedure

After description of the study to the participants, written informed consent was obtained. If eligible, participants performed three tasks in the fMRI scanner, with the emotional faces task always first. Results on the other tasks are reported elsewhere (Van den Berg et al., 2018). Prior to scanning, children < 18 years were familiarized with the scanner environment using a mock scanner. The full protocol was conducted according to the principles expressed in the Declaration of Helsinki, and approved by the Medical Ethics Committee of the Leiden University Medical Center (LUMC).

Measures

Childhood maltreatment

To assess experienced childhood abuse and neglect by mother and/or father, adapted versions of the Conflict Tactics Scales (CTS; Straus et al., 1998) were administered in combination with the emotional neglect scale from the Childhood Trauma Questionnaire (CTQ-SF; Bernstein et al., 2003; see also Compier-de Block, 2017). Parents also completed a CTS version to assess their own abusive or neglectful behaviors towards (each of) their child(ren). An overall *Neglect*-score was calculated by averaging Emotional and Physical Neglect, and an overall *Abuse*-score by averaging Emotional and Physical Abuse. For our analyses we combined information from two informants (parents and offspring) whenever possible (see Supplement for more information), resulting in a total of 285 informants on experienced childhood maltreatment of 171 participants and 184 informants on perpetrated maltreatment of 100 participants. Internal consistencies of the scales were as follows: α-mother = .93 and α-father = .93 for physical abuse, α-mother = .80 and α-father = .77 for emotional abuse, α-mother = .76 and α-father = .65 for physical neglect, and α-mother = .92 and α-father = .91 for emotional neglect. Because the distributions of CTS scores were skewed, scores were logarithmically transformed. Outliers (i.e., values with a standardized value of +/- 3.29), were winsorized to the most extreme value within the normal range plus or minus the difference between the two most extreme values within the normal range (for abuse (n = 1) and neglect history (n = 1).

Emotional faces task

The emotional faces task was based on a paradigm used in previous work (Van Harmelen et al., 2013) that has been found to activate a number of brain regions that are involved in emotion processing, including the amygdala, hippocampus, insula and IFG (e.g., Fusar-Poli et al., 2009; Sabatinelli et al., 2011). E-prime software (Psychological Software Tools, Pittsburgh, PA, USA) was used to present this task using an event-related design. Photographs of 10 women and 10 men were selected from the Radboud Faces Database (Langner et al., 2010) for angry, fearful, surprised, happy and neutral faces. 66 scrambled faces with an arrow in the middle pointing left (50%) or right (50%) were presented as a baseline measure. In total, 166 stimuli were presented against a black background. Each photograph was shown on the screen for 2.5 s, with an inter-stimulus (black screen) interval varying between 0.5 and 1.5 s. Each particular face was presented only once. Stimuli were projected on a screen at the end of the scanner and were visible via a mirror positioned on the head coil. Participants were instructed to indicate whether they saw a man or woman in the photographs by pressing one of two buttons, and when presented with a scrambled face, whether the arrow was pointing left or right.

Covariates

Demographic information (age, gender, handedness and household social economic status (SES)) was assessed using questionnaires. To control for level of psychopathology, three widely used versions of Achenbach's screening tools were used. For participants younger than 12 years old their parents filled out the Child Behavioral Checklist (CBCL; Achenbach, 1991a). The Youth Self Report (YSR; Achenbach, 1991b) was completed by participants from 12 to 17 years. The Adult Self Report (ASR; Achenbach and Rescorla, 2003) was used from 17 years up. For all three instruments a total psychopathology symptom score was calculated. Cronbach's alphas were good to excellent (.76–.93; see Supplement). Of all participants from 17 years and up 7–14% reported symptoms in the subclinical or clinical range on the anxious/depressed, withdrawn, somatic complaints, aggressive behavior, rule-breaking behavior and/or the intrusive subscale of the ASR (Achenbach and Rescorla, 2003; see Supplement Table S1). In the group of younger participants (< 17 years) 3–16% reported symptoms in the subclinical or clinical range on the following subscales of the CBCL (Achenbach, 1991a) or YSR (Achenbach, 1991b): anxious/depressed, withdrawn, aggressive behavior, rule-breaking behavior, somatic complaints, thought problems, attention problems, social problems and other problems (see Supplement Table S2).

fMRI data acquisition

Scanning was performed using a whole-head coil on a 3.0-Tesla Philips Achieva scanner (Philips Medical Systems, Best, The Netherlands) located at the LUMC. Head motion was restricted using foam inserts that surrounded the head. For all participants, T2*-weighted echo-planar images (EPI) were obtained [repetition time (TR) = 2200 ms, echo time (TE) = 30 ms, matrix size: 80 × 79, 38 transverse slices of 2.75 mm, slice gap = 0.28 mm, field of view (FOV) = 220]. In accordance with the LUMC policy, a radiologist from the Radiology department examined all anatomical scans. No incidental findings were reported.

fMRI data preprocessing

Functional imaging data were preprocessed and analyzed using Statistical Parametric Mapping version 8 (SPM8; Wellcome Department of Cognitive Neurology, London) software implemented in Matlab 5.0.7 (Mathworks, Sherborn, MA). After extensive quality control of the data, preprocessing consisted of the following steps: manually reorienting the functional images to the anterior commissure, slice time correction, image realignment, registration of the T1-scan to the mean echo-planar image, warping to Montreal Neurological Institute (MNI)-space as defined by the SPM8 T1-template, reslicing to 3 × 3 × 3 mm voxels and spatial smoothing with a Gaussian kernel (8 mm, full width at half-maximum). Subject movement (>3 mm) resulted in exclusion of the data from further analysis (n = 9).

fMRI data analysis

Data were analyzed using the General Linear Model in SPM8. The fMRI time series data were modeled by a series of events convolved with a canonical hemodynamic response function (HRF). The picture presentation of each emotional face was modeled as a zero duration event. Low-frequency noise was removed by applying a high-pass filter (cut-off 120 s) to the fMRI time series at each voxel. Statistical parametric maps for each comparison of interest were calculated on a voxel-by-voxel basis. For each subject, the following contrasts were computed: angry > scrambled, fearful > scrambled, happy > scrambled, neutral > scrambled and all expressions > scrambled. Surprised faces were not of interest for the current study and therefore not included in separate analyses. To investigate the neural correlates of emotional face processing, four anatomical key regions of interest (ROIs) were defined using the automatic anatomical labeling (AAL) toolbox within the Wakeforest-pickatlas toolbox (Maldjian et al., 2003): the amygdala, hippocampus, IFG and insula. See below for more details. All results are reported in MNI space.

SPSS data analysis

Brain activity was examined with three-level multilevel regression analyses in which participants were nested within households and households were nested within families, using SPSS 23, to take the family structure of the data into account. In this approach, level 1 models variation at the participant (individual) level, level 2 estimates variation among participants within the same household, and level 3 captures variation among families. Random intercept models were built sequentially, starting with an empty (null) model without explanatory variables in which the total variance of brain reactivity in response to faces was partitioned into a component at each level. This empty model was used to test for random variation of the outcome variables at the different levels. Most, but not all, of the reported intraclass correlations (ICCs) were low (see Supplement). To control for the nested structure of data we decided to consistently use multilevel analyses for all ROIs. In the next model, age, gender, handedness, SES and psychopathology were added as covariates to the model to control for these factors. Only significant covariates ($p < .05$) were kept in the final model. Because of the large age range and our focus on age, age was always included as a covariate. To explore fixed effects of abuse and neglect, main effects of abuse and neglect were added to Model 1, and interaction effects of age × abuse and age × neglect in Model 2. In case of significant interaction effects between experienced maltreatment and age we split up the sample in participants up to 18 years old (children and adolescents who are generally still living at home with their parents) and participants older than 18 years old (generally living on their own) for illustrative purposes only. Multilevel regression analyses were run for each of our four ROIs (the amygdala, hippocampus, IFG and insula) for fearful, angry, happy and neutral faces separately. Separate analyses were run for severity of maltreatment history (all participants: $n = 171$) and for severity of

maltreating parenting behavior (participants with offspring: $n = 100$). All (continuous) predictor variables and covariates were centered. All independent and dependent variables were measured at the individual level (except SES) and considered in the fixed part of the model. Unstandardized regression coefficients are reported.

RESULTS

Table 1 shows demographics and mean (SD) maltreatment scores. Pearson correlations were calculated between all variables (see Supplement). The correlation between experienced abuse and neglect was $r = .57$ ($p < .001$), whereas abusive and neglectful behavior were also moderately associated ($r = .32$, $p < .001$). To examine intergenerational transmission of maltreatment in our sample, regression analyses were conducted with experienced childhood abuse and neglect as predictors and with abusive and neglectful behavior as outcome measures for participants with offspring ($n = 100$ parents). Results indicated that, controlling for age, gender, household SES and psychopathology in the first block, experienced abuse ($\beta = .55$, $t(93) = 5.35$, $p < .001$) was the only significant predictor of perpetrated abuse. Experienced neglect did not predict perpetrated abuse ($p = .122$). None of the covariates were significant. Perpetrated neglect was not predicted by

Table 1. Demographics, psychopathology, and maltreatment scores ($n = 171$).

Variables	Mean (SD)	Range
Age	35.14 (16.60)	8.25 - 69.67
Gender (*n:* men/women)	73/98	–
Handedness (*n*: left/right)	22/149	–
CBCL	12.79 (7.02)	3.00 - 28.50
YSR	20.00 (14.70)	0.00 - 46.00
ASR	24.56 (15.51)	1.00 - 83.00
Abused[a]	1.62 (0.48)	1.00 - 4.50
Neglected[a]	1.86 (0.58)	1.00 - 5.00
Maltreated[a] (total)	1.74 (0.47)	1.00 - 4.75
Abusive[b] ($n = 100$)	1.48 (0.32)	1.00 - 2.53
Neglectful[b] ($n = 100$)	1.58 (0.32)	1.00 - 2.48
Maltreating[b] (total; $n = 100$)	1.53 (0.26)	1.0 - 2.22

CBCL = Child Behavioral Checklist; YSR = Youth Self Report; ASR = Adult Self Report
[a]Combined experienced maltreatment scores by averaging parent and child reports as measured with the CTS. [b]Combined maltreating behavior scores by averaging parent and child reports as measured with the CTS.
Values of all included participants are presented ($n = 171$) unless otherwise specified.
Raw scores are presented.

experienced neglect (p = .709) nor by experienced abuse (p = .884). Age (β = .21, p = .049) and psychopathology (β = .33, p = .003) were significant covariates for perpetrated neglect.

Face processing

The whole brain analysis for the contrast all expressions versus scrambled faces (baseline) showed significant clusters of activation in brain areas involved in face processing (namely the amygdala, hippocampus, insula and IFG; e.g., Fusar-Poli et al., 2009) at $p < 0.01$ family-wise error (FWE) corrected for multiple comparisons on cluster level with a threshold of 10 or more contiguous voxels (see Supplement for an overview of all activated clusters). We extracted the left and right amygdalae, hippocampi, IFG and insulae as anatomical ROIs using the automatic anatomical labeling (AAL) toolbox within the Wakeforest-pickatlas toolbox (Maldjian et al., 2003) and the MARSBAR toolbox (Brett et al., 2002; see Figure 1). Left and right clusters were combined for all ROIs as there were no effects of laterality.

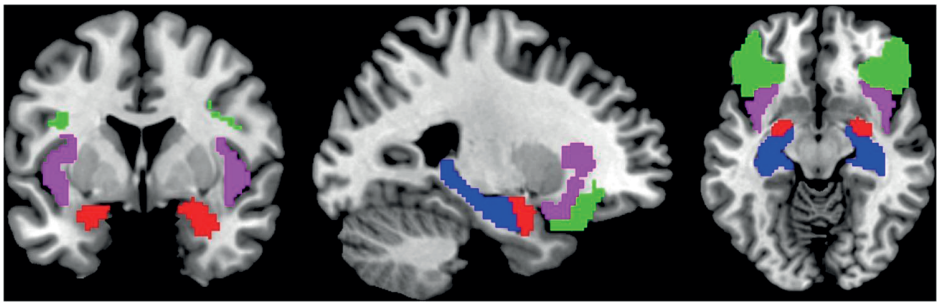


Figure 1. Anatomical ROI masks.
Red: left and right amygdalae; Blue: left and right hippocampi; Green: IFG; Violet: left and right insulae.

Multilevel analyses

In the following section results of our multilevel regression analyses will be described per ROI for severity of maltreatment history (all participants: n = 171) and for severity of maltreating parenting behavior (participants with offspring: n = 100) separately. All multilevel regression analyses were run controlling for age, gender, handedness, SES and psychopathology (see Table 2A-5B).

Amygdala: experienced abuse and neglect

Multilevel analyses were performed with experienced abuse and neglect as predictors and BOLD responses in the amygdala as outcome measure (see Table 2A, and see Supplement for an overview of all significant multilevel analyses results). Analyses were run for fearful, angry, happy and neutral versus scrambled faces separately. No significant main effects were found for abuse or neglect regarding activation in the amygdala for angry, fearful, happy or neutral faces. However, results revealed a significant improvement of the model

when the interactions with age were added for fearful faces (χ^2 (2) = 8.56, p = .014). Younger participants (up to 18 years old) who experienced more neglect showed lower activation in the amygdala while viewing fearful faces than younger participants who experienced less neglect (β = 0.08, t = 2.91, p = .004). For older participants an opposite effect for fearful faces was found, with higher amygdala activation for older participants who experienced more neglect (see Supplement Figure S1 and S2 for a visual representation of the significant interaction effects between experienced maltreatment and age).

Table 2A. Multilevel models of brain reactivity in the left and right amygdalae in response to neutral and emotional faces as related to experienced childhood abuse and neglect (n = 171).

Amygdala ROI												
	Anger			Fear			Happy			Neutral		
	b	SE	*p*	*b*	SE	*p*	*b*	SE	*p*	*b*	SE	*p*
Null model												
age	−0.01	.00	.078	−0.00	.00	.540	−0.00	.00	.269	0.00	.00	.616
gender	0.03	.10	.745	−0.03	.09	.740	0.03	.10	.725	0.04	.11	.689
handedness	−0.20	.15	.177	−0.00	.13	.975	−0.07	.15	.619	0.04	.16	.788
SES	−0.01	.07	.847	0.06	.06	.375	0.10	.07	.159	0.08	.08	.309
PP	−0.00	.24	.984	−0.11	.22	.617	0.01	.24	.970	−0.11	.26	.687
Model 1												
abused	−0.73	.51	.151	−0.61	.46	.182	0.18	.51	.722	0.10	.56	.860
neglected	1.00	.50	.050	0.73	.45	.112	0.07	.51	.883	0.17	.56	.767
	χ^2 (2) = 4.21		.122	χ^2 (2) = 3.00		.223	χ^2 (2) = 0.25		.884	χ^2 (2) = 0.21		.900
Model 2												
abused*age	−0.01	.03	.791	−0.02	.03	.523	−0.01	.03	.723	−0.03	.03	.354
neglected*age	0.05	.03	.098	0.08	.03	.004**	0.02	.03	.416	0.08	.03	.017*
	χ^2 (2) = 2.99		.224	χ^2 (2) = 8.56		.014*	χ^2 (2) = 0.66		.717	χ^2 (2) = 5.75		.057

* p < .05; ** p < .01.

Amygdala: abusive and neglectful behavior

Similar multilevel analyses were run for participants with offspring with abusive and neglectful behavior as predictors (see Table 2B). Results showed no significant main effects for abusive or neglectful behavior nor interaction effects with age for brain reactivity in the amygdala in response to neutral or emotional faces.

Hippocampus: experienced abuse and neglect

Multilevel regression analyses were conducted for fearful, angry, happy and neutral faces separately, with BOLD responses in the hippocampus as outcome measure and experienced abuse and neglect as predictors (see Table 3A). Results showed no significant main

Table 2B. Multilevel models of brain reactivity in the left and right amygdalae in response to neutral and emotional faces as related to abusive and neglectful behavior (n = 100 parents).

Amygdala ROI												
	Anger			Fear			Happy			Neutral		
	b	SE	*p*	*b*	SE	*p*	*b*	SE	*p*	*b*	SE	*p*
Null model												
age	0.00	.01	.459	0.00	.01	.644	0.01	.01	.359	0.00	.01	.496
gender	0.01	.14	.948	−0.10	.11	.359	−0.04	.13	.753	−0.12	.14	.405
handedness	−0.21	.23	.364	0.02	.19	.920	0.01	.21	.962	0.27	.24	.263
SES	−0.04	.09	.630	0.07	.08	.377	0.11	.09	.208	0.06	.10	.585
PP	−0.06	.34	.856	−0.17	.28	.545	−0.18	.32	.562	−0.16	.36	.660
Model 1												
abusive	0.35	.79	.664	−0.08	.66	.900	0.42	.74	.572	0.53	.84	.526
neglectful	0.54	.84	.524	−0.09	.70	.896	−0.36	.78	.642	−0.23	.89	.800
	χ^2 (2) = 0.84		.658	χ^2 (2) = 0.05		.976	χ^2 (2) = 0.41		.815	χ^2 (2) = 0.40		.819
Model 2												
abusive*age	−0.03	.10	.793	−0.04	.08	.606	−0.07	.09	.429	−0.06	.10	.544
neglectful*age	0.03	.08	.729	0.03	.07	.646	0.05	.07	.480	0.07	.09	.418
	χ^2 (2) = 0.13		.937	χ^2 (2) = 0.32		.851	χ^2 (2) = 0.76		.685	χ^2 (2) = 0.70		.703

* $p < .05$; ** $p < .01$.

Table 3A. Multilevel models of brain reactivity in the left and right hippocampi in response to neutral and emotional faces as related to experienced childhood abuse and neglect (n = 171).

Hippocampus ROI												
	Anger			Fear			Happy			Neutral		
	b	SE	*p*	*b*	SE	*p*	*b*	SE	*p*	*b*	SE	*p*
Null model												
age	−0.00	.00	.263	−0.00	.00	.548	−0.00	.00	.710	0.00	.00	.836
gender	−0.02	.07	.804	−0.05	.06	.351	0.03	.07	.701	0.06	.07	.428
handedness	0.01	.10	.941	0.13	.09	.141	−0.01	.11	.950	0.08	.11	.495
SES	−0.03	.05	.502	0.03	.04	.433	0.07	.05	.195	0.10	.05	.065
PP	0.25	.17	.133	0.01	.14	.940	−0.00	.18	.981	0.02	.18	.898
Model 1												
abused	−0.21	.36	.567	−0.41	.31	.188	−0.15	.38	.694	0.30	.38	.433
neglected	0.61	.35	.085	0.50	.31	.104	0.24	.38	.532	−0.06	.38	.868
	χ^2 (2) = 2.99		.224	χ^2 (2) = 3.01		.222	χ^2 (2) = 0.39		.825	χ^2 (2) = 0.66		.718
Model 2												
abused*age	0.01	.02	.763	−0.01	.02	.606	−0.01	.02	.630	−0.03	.02	.232
neglected*age	−0.00	.02	.892	0.02	.02	.235	0.00	.02	.878	0.04	.02	.097
	χ^2 (2) = 0.09		.956	χ^2 (2) = 1.40		.496	χ^2 (2) = 0.23		.890	χ^2 (2) = 3.04		.219

* $p < .05$; ** $p < .01$

effects for experienced abuse or neglect nor interaction effects with age for brain reactivity in the hippocampus in response to neutral or emotional faces.

Hippocampus: abusive and neglectful behavior

Similar multilevel analyses were run for participants with offspring with abusive and neglectful behavior as predictors (see Table 3B). Results showed no significant main effects for abusive and neglectful behavior nor interaction effects with age for brain reactivity in the hippocampus in response to neutral or emotional faces.

Table 3B. Multilevel models of brain reactivity in the left and right hippocampi in response to neutral and emotional faces as related to abusive and neglectful behavior (n = 100 parents).

Hippocampus ROI												
	Anger			Fear			Happy			Neutral		
	b	SE	*p*	*b*	SE	*p*	*b*	SE	*p*	*b*	SE	*p*
Null model												
age	0.00	.00	.726	0.00	.00	.716	0.00	.00	.305	0.00	.00	.395
gender	−0.05	.09	.594	−0.08	.07	.259	−0.01	.09	.888	−0.05	.09	.624
handedness	−0.00	.15	.979	0.28	.12	.020*	0.11	.15	.497	0.27	.16	.095
SES	−0.07	.06	.286	0.01	.05	.794	0.03	.06	.613	0.02	.06	.771
PP	0.30	.23	.180	−0.11	.18	.527	−0.25	.23	.290	−0.11	.23	.651
Model 1												
abusive	0.58	.52	.270	0.04	.42	.931	−0.17	.54	.759	−0.05	.55	.925
neglectful	0.76	.55	.174	−0.09	.44	.846	−0.07	.57	.901	−0.16	.59	.786
	χ^2 (2) = 4.28		.117	χ^2 (2) = 0.04		.981	χ^2 (2) = 0.15		.927	χ^2 (2) = .11		.946
Model 2												
abusive*age	0.02	.06	.801	−0.01	.05	.782	0.04	.06	.531	−0.05	.07	.411
neglectful*age	0.06	.05	.261	0.01	.04	.887	0.05	.05	.371	0.10	.06	.085
	χ^2 (2) = 2.11		.349	χ^2 (2) = 0.08		.962	χ^2 (2) = 2.34		.310	χ^2 (2) = 2.99		.225

* $p < .05$; ** $p < .01$.

IFG: experienced abuse and neglect

Multilevel regression analyses were done for fearful, angry, happy and neutral faces separately, with BOLD responses in the IFG as outcome measure and experienced abuse and neglect as predictors (see Table 4A). No significant main effects were found for abuse or neglect regarding activation in the IFG. However, results revealed a significant improvement of the model when the interactions with age were added for fearful (χ^2 (2) = 8.25, p = .016), happy (χ^2 (2) = 9.46, p = .009) and neutral faces (χ^2 (2) = 8.92, p = .012). All three interaction effects revealed the same interaction pattern. Younger participants who experienced more abuse showed lower activation in the IFG while viewing fearful (β = 0.05, t = 2.23, p = .027), happy (β = 0.05, t = 2.26, p = .025) and neutral faces (β = 0.06, t = 2.41, p =

Table 4A. Multilevel models of brain reactivity in the IFG in response to neutral and emotional faces as related to experienced childhood abuse and neglect (*n* = 171).

IFG ROI												
	Anger			Fear			Happy			Neutral		
	b	SE	*p*	*b*	SE	*p*	*b*	SE	*p*	*b*	SE	*p*
Null model												
age	−0.00	.00	.555	−0.00	.00	.491	0.00	.00	.802	−0.00	.00	.203
gender	0.00	.08	.972	0.01	.07	.910	0.11	.07	.122	0.13	.07	.078
handedness	0.10	.12	.421	0.06	.11	.595	−0.04	.11	.698	0.05	.11	.643
SES	0.00	.06	.982	−0.00	.06	.996	0.09	.05	.073	0.09	.06	.090
PP	−0.04	.20	.843	−0.13	.19	.483	−0.18	.18	.302	0.09	.18	.631
Model 1												
abused	−0.54	.43	.207	−0.77	.40	.057	−0.28	.38	.473	−0.33	.40	.406
neglected	0.40	.42	.340	0.07	.39	.856	0.06	.38	.873	0.55	.40	.168
	χ^2 (2) = 1.79		.409	χ^2 (2) = 3.91		.142	χ^2 (2) = 0.55		.761	χ^2 (2) = 1.92		.383
Model 2												
abused*age	0.04	.02	.116	0.05	.02	.027*	0.05	.02	.025*	0.06	.02	.017*
neglected*age	−0.04	.02	.126	−0.06	.02	.008**	−0.06	.02	.004**	−0.06	.02	.007**
	χ^2 (2) = 3.32		.191	χ^2 (2) = 8.25		.016*	χ^2 (2) = 9.46		.009**	χ^2 (2) = 8.92		.012*

* $p < .05$; ** $p < .01$.

.017) than younger participants who experienced less abuse. For older participants there was no effect of experienced abuse on activation in the IFG.

For neglect we found an opposite effect in younger individuals. Younger participants who experienced more neglect showed higher activation in the IFG while viewing fearful (β = −0.06, t = −2.68, p = .008), happy (β = −0.06, t = −2.91, p = .004) and neutral faces (β = −0.06, t = −2.71, p = .007) than younger participants who experienced less neglect. For older participants there was no effect of experienced neglect on activation in the IFG for fearful, happy or neutral faces.

IFG: abusive and neglectful behavior

Similar multilevel analyses were performed for all participants with offspring with abusive and neglectful behavior as predictors (see Table 4B). Results showed no significant main effects for abusive or neglectful behavior nor interaction effects with age for brain reactivity in the IFG in response to neutral or emotional faces.

Insula: experienced abuse and neglect

Multilevel regression analyses were run for fearful, angry, happy and neutral faces separately, with BOLD responses in the insula as outcome measure and experienced abuse and neglect as predictors (see Table 5A). Results showed no significant main effects for

Table 4B. Multilevel models of brain reactivity in the IFG in response to neutral and emotional faces as related to abusive and neglectful behavior (n = 100 parents).

IFG ROI												
	Anger			Fear			Happy			Neutral		
	b	SE	*p*	*b*	SE	*p*	*b*	SE	*p*	*b*	SE	*p*
Null model												
age	0.00	.01	.384	0.00	.00	.858	0.01	.00	.060	−0.00	.00	.878
gender	−0.03	.11	.791	0.06	.08	.450	−0.02	.08	.829	0.05	.10	.629
handedness	0.05	.19	.777	−0.32	.13	.014*	−0.13	.14	.370	0.04	.17	.822
SES	0.01	.08	.891	0.03	.05	.550	0.03	.06	.574	0.06	.07	.413
PP	−0.27	.28	.332	−0.52	.19	.008**	−0.52	.21	.015*	0.00	.26	.996
Model 1												
abusive	1.10	.64	.087	0.24	.46	.608	0.38	.50	.447	0.57	.61	.352
neglectful	0.37	.68	.587	0.40	.48	.413	0.38	.52	.468	0.29	.64	.658
	χ^2 (2) = 4.27		.118	χ^2 (2) = 1.28		.528	χ^2 (2) = 1.51		.471	χ^2 (2) = 1.49		.474
Model 2												
abusive*age	0.02	.08	.748	−0.02	.05	.659	0.03	.06	.664	0.05	.07	.505
neglectful*age	0.06	.06	.333	0.01	.04	.792	0.05	.05	.273	−0.05	.06	.460
	χ^2 (2) = 1.81		.405	χ^2 (2) = 0.20		.906	χ^2 (2) = 2.49		.289	χ^2 (2) = 0.61		.738

* p < .05; ** p < .01.

Table 5A. Multilevel models of brain reactivity in the left and right insulae in response to neutral and emotional faces as related to experienced childhood abuse and neglect (n = 171).

Insula ROI												
	Anger			Fear			Happy			Neutral		
	b	SE	*p*	*b*	SE	*p*	*b*	SE	*p*	*b*	SE	*p*
Null model												
age	−0.00	.00	.064	−0.00	.00	.043*	−0.00	.00	.241	−0.00	.00	.150
gender	0.02	.06	.807	0.00	.06	.934	0.07	.06	.252	0.13	.06	.038*
handedness	0.05	.10	.579	0.17	.09	.057	0.04	.09	.675	0.19	.09	.044*
SES	−0.01	.05	.778	−0.01	.04	.745	0.04	.04	.312	0.09	.04	.043*
PP	0.07	.16	.650	−0.07	.15	.649	−0.14	.15	.367	0.10	.15	.494
Model 1												
abused	−0.12	.33	.719	−0.51	.31	.106	−0.30	.33	.366	0.04	.33	.896
neglected	0.37	.33	.266	0.36	.31	.243	0.36	.32	.260	0.24	.33	.462
	χ^2 (2) = 1.27		.531	χ^2 (2) = 2.72		.257	χ^2 (2) = 1.46		.483	χ^2 (2) = 0.80		.671
Model 2												
abused*age	0.02	.02	.393	0.02	.02	.232	0.03	.02	.097	0.02	.02	.315
neglected*age	−0.01	.02	.461	−0.03	.02	.067	−0.04	.02	.022*	−0.02	.02	.403
	χ^2 (2) = 0.90		.638	χ^2 (2) = 3.56		.169	χ^2 (2) = 5.81		.055	χ^2 (2) = 1.21		.545

* p < .05; ** p < .01.

experienced abuse or neglect nor interaction effects with age for brain reactivity in the insula in response to neutral or emotional faces.

Insula: abusive and neglectful behavior

Multilevel analyses were repeated for all participants with offspring with abusive and neglectful behavior as predictors (see Table 5B). Results showed no significant main effects for abusive or neglectful behavior nor interaction effects with age for brain reactivity in the insula in response to neutral or emotional faces.

Table 5B. Multilevel models of brain reactivity in the left and right insulae in response to neutral and emotional faces as related to abusive and neglectful behavior (*n* = 100 parents).

Insula ROI												
	Anger			Fear			Happy			Neutral		
	b	SE	*p*	*b*	SE	*p*	*b*	SE	*p*	*b*	SE	*p*
Null model												
age	0.00	.00	.787	−0.00	.00	.224	0.00	.00	.763	−0.01	.00	.117
gender	−0.07	.08	.408	−0.09	.06	.170	−0.08	.07	.218	0.05	.08	.567
handedness	0.07	.14	.599	0.08	.11	.435	−0.01	.11	.929	0.20	.13	.130
SES	−0.01	.06	.917	0.02	.04	.648	0.01	.05	.869	0.04	.05	.422
PP	−0.01	.21	.969	−0.07	.16	.667	−0.38	.17	.028*	0.05	.20	.798
Model 1												
abusive	0.44	.48	.355	0.29	.37	.444	−0.17	.40	.680	0.26	.47	.584
neglectful	0.26	.51	.606	−0.33	.39	.401	0.12	.43	.775	−0.19	.50	.699
	χ^2 (2) = 1.61		.448	χ^2 (2) = 0.98		.613	χ^2 (2) = 0.21		.903	χ^2 (2) = 0.35		.839
Model 2												
abusive*age	0.04	.06	.536	0.00	.04	.983	0.06	.05	.236	0.00	.06	.948
neglectful*age	0.05	.05	.328	0.02	.04	.526	0.04	.04	.358	0.01	.05	.819
	χ^2 (2) = 2.60		.273	χ^2 (2) = 0.56		.756	χ^2 (2) = 4.41		.110	χ^2 (2) = 0.09		.956

* $p < .05$; ** $p < .01$.

DISCUSSION

The current study is the first to examine the role of neural reactivity to emotional faces in the intergenerational transmission of childhood maltreatment using a large multi-generational family study design. Our findings indicate that neural activation in the amygdala and IFG are associated with experienced childhood maltreatment, but not with maltreating behavior. Moreover, our results point to somewhat differential effects for experienced abuse and neglect, depending on current age.

Experienced abuse and neglect

As expected and in line with previous studies (e.g., Maheu et al., 2010; Van Harmelen et al., 2013), our results showed that adults who experienced childhood neglect exhibited enhanced bilateral amygdala activation in response to fearful faces, indicating hypervigilance to negatively valenced faces in neglected adults. However, this hypervigilance was only observed in older neglected individuals, and in contrast, younger neglected individuals showed lower amygdala activation when fearful faces were presented compared to young, non-neglected individuals. Increased amygdala reactivity in neglected adults is in line with other imaging studies in adults (Van Harmelen et al., 2013). Decreased amygdala activation in younger neglected individuals is in line with offspring from risky families showing little amygdala activation during the observation of emotional faces (Taylor et al., 2006). This might suggest that younger individuals, still living at home with their (possibly neglectful) parents, experience a form of disengagement or even emotional avoidance of emotional, or in our study, fearful faces. Against our expectations, amygdala and hippocampus activation was not associated with experienced abuse. This is not in line with other studies, where associations have been reported between, for example, experienced physical abuse and heightened right amygdala reactivity (e.g., Grant et al., 2011). These discrepant findings might be due to the fact that most previous studies did not disentangle abuse and neglect (e.g., Hart and Rubia, 2012). Although a recent meta-analysis showed that neglect is the most prevalent type of maltreatment and long-term effects of neglect seem to be at least as important as those of abuse, it is striking that neglect still is an understudied form of maltreatment (e.g., Stoltenborgh et al., 2013). Altered neural reactivity to emotional faces associated with neglect emphasizes the importance to specifically focus on the neural correlates of neglect in future research.

Our results further showed that activity in the IFG for fearful, happy and neutral faces was associated with experienced abuse and neglect, dependent on the age of participants. In younger maltreated individuals, we found that younger abused individuals showed lower activation in the IFG while viewing fearful, happy and neutral faces, whereas younger neglected individuals showed higher activation in the IFG while viewing these faces. These effects disappeared with increasing age, since no associations between experienced abuse or neglect were found with activation in the IFG while viewing emotional or neutral faces for older participants.

The finding that experiences of abuse and neglect were associated with altered IFG reactivity was found irrespective of valence, is consistent with studies reporting that neglected children have poor valence discriminatory abilities for emotional faces (e.g., Pollak et al., 2000; Vorria et al., 2006; Van Harmelen et al., 2013). Additionally, altered processing of positive emotions (happy faces) in maltreated individuals is in line with results of previous research (Koizumi and Takagishi, 2014). The IFG is considered as one of the core regions of emotional face processing and is associated with attentional control (e.g.,

Hampshire et al., 2010; Sabatinelli et al., 2011). Our findings may suggest that neglected children have to work harder to process emotional faces since neglectful parents offer fewer opportunities to their children in learning to interpret emotional signals. On the contrary, abused children are more often exposed to behavior that may induce fear and hypervigilance which might explain our opposite findings regarding experienced abuse and neglect (Crittenden, 1981; Bousha and Twentyman, 1984; Pollak et al., 2000).

Age effects

Independent of abuse and neglect experiences, older participants exhibited lower activation in the insula while viewing fearful faces than younger participants. This is consistent with previous findings, although these studies included smaller samples with a more restricted age range (e.g., Gunning-Dixo et al., 2003). Interestingly, all effects of experienced abuse and neglect on neural reactivity to emotional and neutral faces were moderated by age. Taken together, this seems to indicate age-dependent sensitivity of the amygdala and IFG during face perception in maltreated individuals. While amygdala reactivity in response to fearful and neutral faces showed an opposite effect in younger (decreased activation) versus older (increased activation) neglected individuals, in older abused and neglected individuals the neural effects in the IFG seemed to disappear with increasing age. A possible explanation for these age effects could be that children or adolescents up to 18 years old are generally still living at home with their (possibly maltreating) parents, which is not the case for older individuals. Altered brain reactivity to emotional faces in these younger individuals might reflect temporary adaptation to or coping with current threat which disappears with time, when one leaves the threatening situation at home. Also, depending on age, experienced maltreatment may be perceived in different ways, as there may be cohort effects, alteration of memories with time in older individuals, or other buffering factors in older people who are not currently experiencing maltreatment (e.g. having been in therapy). There may have also been effects of timing of the experienced maltreatment on developmental windows for some brain regions, which might have contributed to our findings, particularly in the IFG. So far, a clear developmental perspective across the life span on the neural basis of emotion processing in maltreated individuals is missing, and our findings emphasize that future research using samples with a large age range might reveal important new insights on this topic.

Abusive and neglectful behavior

Parental abusive or neglectful behavior was not associated with bilateral amygdala, hippocampus, IFG or insula activation in response to emotional or neutral faces, even though some functional imaging studies have suggested these brain areas might play a role in (dysfunctional) parenting behavior (e.g., Atzil et al., 2011; Barrett and Fleming, 2011). Previous research showed that intrusive mothers exhibited higher activation to their own

infant's cry sounds in the insula (Musser et al., 2012) – however, cry sounds of their own child were used as a stimulus, which may explain the different results. Other studies also made use of idiosyncratic stimuli of one's own infants that might specifically activate attachment representations (Barrett and Fleming, 2011) instead of the unfamiliar and non-infant pictures of adult faces as presented in the current study. To further explore whether parental maltreatment is predominantly associated with altered processing of emotions in the family context, future research that investigates neural reactivity to both familiar and unfamiliar faces is recommended. In addition, the age effects in abused and neglected individuals in the IFG and insula indicate that altered neural responses to emotional and neutral faces fade during adolescence and adulthood, which might explain the absence of associations between maltreating behavior and neural reactivity to emotional faces in our results. Another possible explanation for our results could be that the levels of abusive and neglectful behavior in our sample were not high enough to observe significant differences in neural reactivity. Future research should focus on also including participants who show higher levels of maltreating behavior to investigate this hypothesis.

Intergenerational transmission of maltreatment

In the sample of the current study we found intergenerational transmission of abuse in our behavioral results, whereas transmission of neglect was not observed. However, this is likely due to the smaller sample size of the imaging study, since we did find evidence for intergenerational transmission of neglect in the total sample of the 3 G study (n = 202). On a neural level, altered neural reactivity to emotional and neutral faces in the amygdala and IFG was associated with experienced abuse and neglect, but not with abusive or neglectful behavior. Hence, no neural mechanisms playing a role in the transmission of maltreatment were found in these brain areas.

Strengths and limitations

Our study is the first multi-informant, multi-generation family study on child maltreatment in which potentially differential neural effects of abuse and neglect on emotional face processing are examined. Research on the neural correlates of child maltreatment, and maltreating parenting behavior in particular, is scarce, and our family design enables the examination of intergenerational transmission within families directly. A further strength of the current study is that we combined parent (both fathers and mothers) and child reports in the maltreatment scores, which may diminish the influence of individual reporter bias. A limitation of the current study is the use of retrospective reports to measure maltreatment, which can be subject to recall bias. However, we combined parent and child reports in the maltreatment scores and research shows that maltreatment history is more likely to be under- than over-reported (e.g., Hardt and Rutter, 2004). Furthermore, our sample to examine the effects of perpetrated maltreatment was smaller than our

sample to assess the effects of experienced maltreatment since only part of the sample were parents. Hence, the stronger effects that were found in association with experienced abuse and neglect rather than with abusive and neglectful behavior may also be due to differences in sample size. Another limitation of the current study is the high number of analyses. We have chosen for these exploratory analyses without strict correction of the alpha level since this is the first study to examine the role of neural reactivity to emotional and neutral faces in the transmission of maltreatment, using a multi-generational family design with an age range this large. However, we are aware that the current findings require replication before strong conclusions can be drawn.

CONCLUSION

In sum, neural reactivity to emotional and neutral faces in the amygdala and IFG was associated with experienced maltreatment (abuse and neglect) but not with maltreating (abusive and neglectful) behavior. Hence, we found no indications for a role of neural reactivity to emotional faces in the intergenerational transmission of abuse and neglect. Moreover, we found differential effects of experienced abuse and neglect on neural reactivity to emotional faces. This might be related to the fact that neglectful parents offer fewer opportunities to their children in learning to interpret emotional signals, whereas abusive parents interact with their children more often, but also expose them to behavior that may induce fear and hypervigilance (Crittenden, 1981; Bousha and Twentyman, 1984; Pollak et al., 2000). Our study highlights the importance to distinguish between maltreatment subtypes in research and clinical practice. A further strength of our study was the large age range of our sample (8–69 years) and the significant age effects that could be observed as a result. Further identification of the age-dependent alterations in emotion processing in individuals with experienced and perpetrated abuse and neglect is important to ultimately unravel the mechanisms involved in abuse and neglect and design and implement effective preventive interventions.

CONFLICT OF INTEREST

None declared.

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AUTHOR CONTRIBUTIONS

Conceived and designed the experiments: LJMvdB MST MJBK BME. Performed the experiments: LJMvdB LHCGCdB. Analyzed the data: LJMvdB MST MJBK BME. Wrote the paper: LJMvdB MST LHCGCdB MJBK BME.

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SUPPLEMENT

Participants

The total sample of participants for the current study included four parent-child pairs with two parents and two children (*n* = 16), 12 pairs with two parents and one child (*n* = 36), 11 pairs with one parent and two children (*n* = 33), 17 pairs with one parent and one child (*n* = 34) and one pair with two children and three parents (two biological parents and a step-father; *n* = 5). Additionally, 36 parents participated without their children and 11 children participated without their parents participating.

The vast majority of all participants (97%) were Caucasian, four participants were of Latin-American descent and two of mixed descent. Elementary school or a short track of secondary school was completed by 27% of all participants, 35% held an advanced secondary school or vocational school diploma, 18% held a college or university degree and 7% a postgraduate diploma. 8% of all participants were still in elementary school. Education level of 5% was unknown, but most of these participants were under 17 years old.

Childhood maltreatment

The CTS consists of 22 items encompassing four subscales. *Psychological Aggression* (i.e. emotional abuse; 5 items) assesses verbal or other non-physical communication aimed at inflicting psychological pain or fear on the child (e.g., "threatened to spank or hit"). *Physical Assault* (i.e. physical abuse) consists of 13 items, including corporal punishment, severe assault, and very severe assault. The *Neglect* scale (5 items) measures the failure of a parent to "engage in behavior that is necessary to meet the developmental needs of a child, such as not providing adequate food or supervision" (Straus et al., 1998, p. 253). We excluded the *Nonviolent Discipline* scale (4 items), because none of the items are related to maltreatment. Since this scale includes only one item on emotional neglect (failure to show or tell your child you love them), we added the five items of the *Emotional Neglect* scale from the Childhood Trauma Questionnaire (CTQ-SF; Bernstein et al., 2003). As a consequence, the *Emotional Neglect* scale consisted of six items. To match the response categories of the CTS and CTQ, we used a 5-point scale ranging from "never" (1) to "(almost) always" (5) for all items.

For experienced childhood maltreatment, four subscale scores (*Emotional* and *Physical Abuse*, and *Emotional* and *Physical Neglect*) were calculated from participants' self-reported experienced maltreatment by their parents. Subscale scores comprised the highest score for father or mother (e.g., *Emotional Abuse by father* and *Emotional Abuse by mother* were calculated, and the highest of the two was used to comprise the scale *Emotional Abuse*). Next, an overall *Neglect*-score was calculated by averaging Emotional and Physical Neglect, and an overall *Abuse*-score by averaging Emotional and Physical Abuse.

In the same way, scale scores were calculated for their parents' self-reported maltreating behavior. Finally, we calculated *Experienced Abuse* and *Experienced Neglect* scores by averaging parent's report and child's reports of abuse and neglect. A similar procedure was followed for maltreating behavior (*Parent-to-child maltreatment*), but scale scores for parent-reported maltreating behavior comprised the highest score concerning any one of the children. Child-reported maltreating behavior concerned only the parent in question. Table S7 and S8 provide an overview of the occurrence of self-reported experienced and perpetrated abuse and neglect in our sample.

For 114 out of 171 participants two informants (participants and their parents) reported on maltreatment history and for 57 participants we had only self-report information on experienced maltreatment, resulting in a total of 285 informants on experienced childhood maltreatment. Of all 171 participants, 100 had at least one child and they also reported on maltreating behavior. For 84 of these 100 participants two informants (participants and their children) reported on maltreating behavior, while for the remaining 12 participants we had only self-report information on maltreating behavior. When it was not clear whether children had reported about their biological parents or their stepparents child-report information was not included ($n = 4$). This resulted in a total of 184 informants on perpetrated maltreatment.

Covariates

The CBCL, YSR and ASR are reliable and valid standardized instruments to examine emotional and behavioral problems (e.g., Hankin and Abramson, 2002; Biederman et al., 2005; Hislop et al., 2008). Cronbach's alphas for the CBCL ($\alpha_{child1} = .89$, $\alpha_{child2} = .76$), YSR ($\alpha = .91$) and ASR ($\alpha = .93$) were good to excellent.

Table S1. Reported psychiatric symptoms by participants from 17 years and up.

ASR subscale	% in the subclinical range	% in the clinical range
Anxious/depressed	2.3	5.3
Withdrawn	9.8	3.8
Somatic complaints	5.3	4.5
Intrusive behavior	6.8	7.5
Rule-breaking behavior	3.0	6.0
Aggressive behavior	3.0	3.8

Table S2. Reported psychiatric symptoms by participants up to 16 years old.

CBCL or YSR subscale	% in the subclinical range	% in the clinical range
Anxious/depressed	3.1	6.3
Withdrawn	6.3	9.4
Somatic complaints	6.3	9.4
Rule-breaking behavior	0.0	6.3
Aggressive behavior	0.0	6.3
Thought problems	6.3	3.1
Attention problems	6.3	6.3
Social problems	0.0	9.4
Other problems	3.1	0.0

Table S3. Variance accounted for (ICCs) on household and family level for the contrast all emotional faces versus scrambled faces.

	AM	HP	IFG	IN
Family level	.000	.016	.081	.000
Household level	.000	.000	.053	.104

AM = left and right amygdalae ROI; HP = left and right hippocampi ROI; IFG = inferior frontal gyrus ROI; IN = left and right insulae ROI

Table S4. Correlations between all predictor variables.

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
1. Age										
2. Gender	-.07									
3. Handedness	.14	.16*								
4. Psychopathology	.08	.02	-.01							
5. SES	.07	.01	-.13	-.18*						
6. Maltreated	.41**	-.01	-.08	.37**	-.11					
7. Abused	.28**	.00	-.06	.37**	-.05	.86**				
8. Neglected	.42**	-.02	-.08	.29**	-.14	.91**	.57**			
9. Maltreating	.26*	-.12	.02	.39**	-.01	.32**	.39**	.20*		
10. Abusive	.13	.00	-.11	.32**	-.06	.43**	.54**	.25*	.81**	
11. Neglectful	.28**	-.20	-.14	.32**	.05	.10	.09	.08	.82**	.32**

* $p < .05$; ** $p < .01$
SES = socioeconomic status
Gender: 0 = men; 1 = women
Handedness: 0 = left; 1 = right

Table S5. Significant clusters for the contrast all emotional faces versus scrambled faces ($n = 171$).

Clusters	Cluster level, number of voxels	*T*	*p*-value	Coordinates		
				x	*y*	*z*
Right amygdala and hippocampus	1075	17.64	< 0.001	21	-7	-14
		12.10	< 0.001	30	2	-23
		11.61	< 0.001	12	-73	10
Left amygdala and hippocampus	178	13.93	< 0.001	-21	-7	-14
		8.75	< 0.001	-27	2	-20
Right IFG and insula	517	12.65	< 0.001	48	14	28
		10.40	< 0.001	48	26	16
		8.04	< 0.001	42	26	-2
Left IFG and insula	99	7.14	< 0.001	-45	17	25
	89	7.09	< 0.001	-42	23	-5
		6.81	< 0.001	-39	26	-14

$p < 0.01$ FWE corrected, 10 voxels
p-values represent FWE cluster-level corrected values

Table S6. Summary of significant multilevel analyses results per emotion for the 4 ROIs.

	Anger		Fear		Happy		Neutral	
	ROI	*b* (SE)	ROI	*b* (SE)	ROI	*b* (SE)	ROI	*b* (SE)
Experienced maltreatment (*n* = 171)								
Model 1								
abused	-	-	-	-	-	-	-	-
neglected	-	-	-	-	-	-	-	-
Model 2								
abused*age	-	-	IFG	0.05 (.02)*	IFG	0.05 (.02)*	IFG	0.06 (.02)*
neglected*age	-	-	AM IFG	0.08 (.03)** -0.06 (.02)**	IFG	-0.06 (.02)**	IFG	-0.06 (.02)**
Maltreating behavior (*n* = 100)								
Model 1								
abusive	-	-	-	-	-	-	-	-
neglectful	-	-	-	-	-	-	-	-
Model 2								
abusive*age	-	-	-	-	-	-	-	-
neglectful*age	-	-	-	-	-	-	-	-

* $p < .05$; ** $p < .01$

AM = left and right amygdalae ROI; HP = left and right hippocampi ROI; IFG = inferior frontal gyrus ROI; IN = left and right insulae ROI

Table S7. Occurrence of self-reported experienced emotional and physical abuse and neglect.

	Never	Once	More than once
Abuse	6 (4%)	4 (2%)	161 (94%)
Physical Abuse	31 (18%)	21 (12%)	119 (70%)
Emotional Abuse	13 (8%)	6 (4%)	152 (88%)
Neglect	4 (2%)	1 (1%)	166 (97%)
Physical Neglect	110 (64%)	15 (9%)	46 (27%)
Emotional Neglect[a]	4 (2%)	1 (1%)	166 (97%)

Children reported about mother and father.

Occurrences are based on items describing concrete parenting behaviors rather than the overall scales.

[a] Note that four of the emotional neglect items were recoded. This means that participants who 'never' experienced emotional neglect, reported that they '(almost) always' felt emotionally supported.

Table S8. Occurrence of self-reported perpetrated emotional and physical abuse and neglect.

	Never	Once	More than once
Abuse	0 (0%)	1 (1%)	99 (99%)
Physical Abuse	27 (16%)	17 (10%)	56 (74%)
Emotional Abuse	0 (0%)	1 (1%)	99 (99%)
Neglect	6 (4%)	7 (4%)	87 (92%)
Physical Neglect	63 (37%)	28 (16%)	9 (47%)
Emotional Neglect	7 (4%)	9 (5%)	84 (91%)

Parents reported about up to three children. As the number of children varied across parents, occurrence was based on the highest child score.
Occurrences are based on items describing concrete parenting behaviors rather than the overall scales.

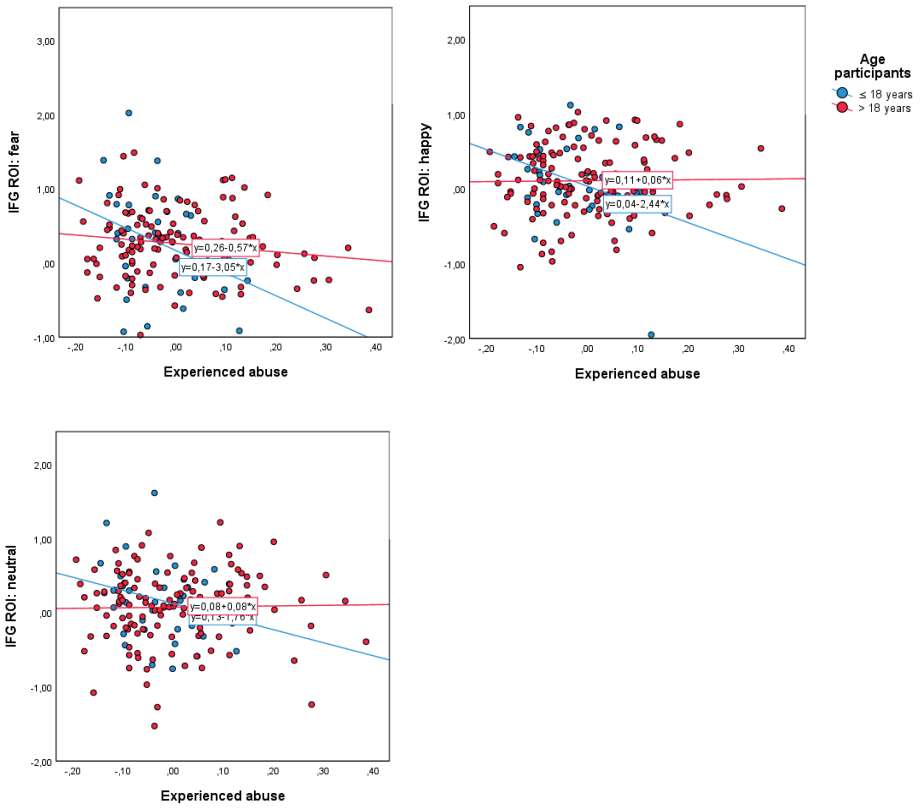


Figure S1. Visual representation of the significant interaction effects between experienced abuse and age for the IFG.

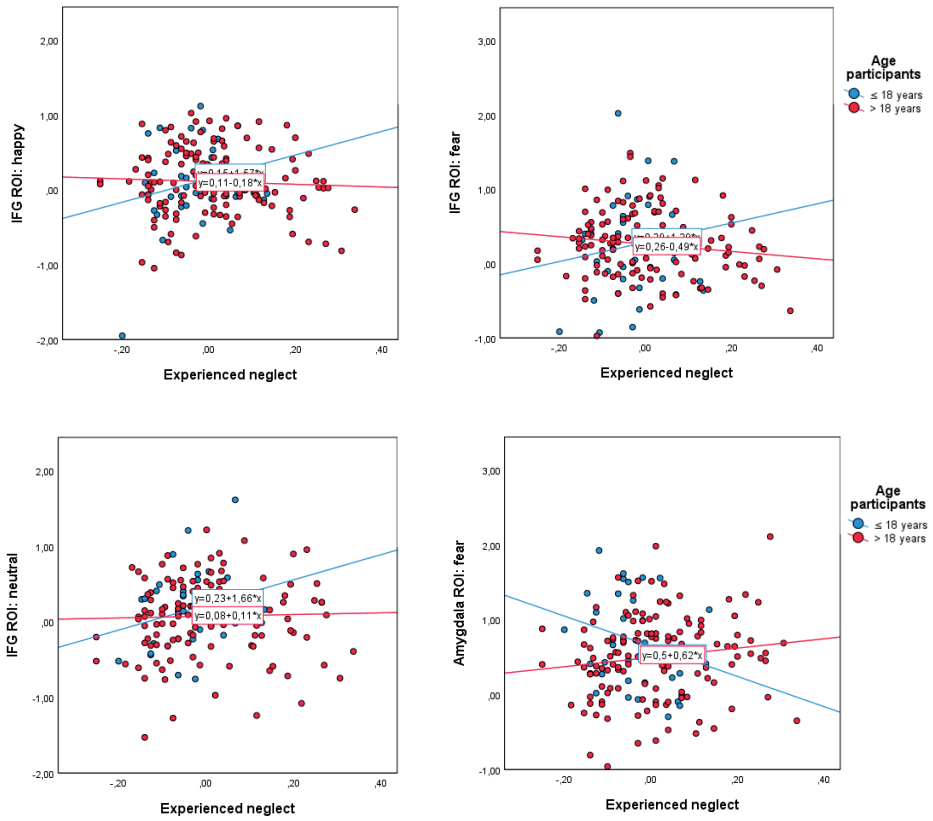


Figure S2. Visual representation of the significant interaction effects between experienced neglect and age for the IFG (A) and amygdala (B).

REFERENCES SUPPLEMENT

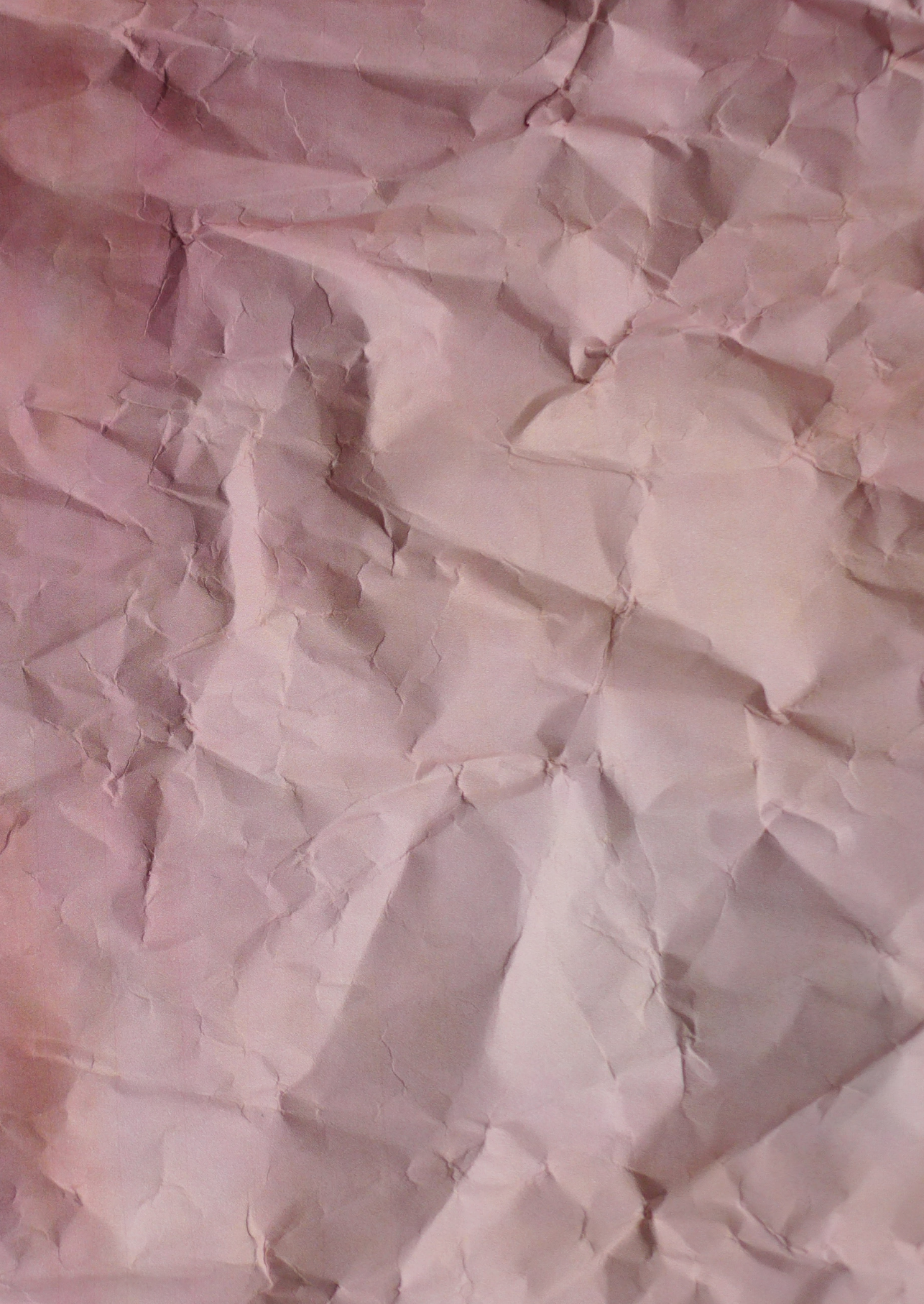
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Chapter 5

Pass it on? The neural responses to rejection in the context of a family study on maltreatment

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ABSTRACT

Background. Rejection by parents is an important aspect of child maltreatment. Altered neural responses to social rejection have been observed in maltreated individuals.

Methods. The current study is the first to examine the impact of experienced and perpetrated abuse and neglect on neural responses to social exclusion by strangers versus family using a multigenerational family design, including 144 participants. The role of neural reactivity to social exclusion in the intergenerational transmission of maltreatment was also examined.

Results. Exclusion by strangers was especially associated with increased activation in the left insula, while exclusion by a family member was mainly associated with increased activation in the ACC. Neural reactivity to social exclusion by strangers in the insula, ACC and dmPFC, was associated with experienced maltreatment but not with perpetrated maltreatment. In abusive parents, altered neural reactivity during exclusion was found in other brain areas, indicating different neural correlates of experienced and perpetrated maltreatment.

Conclusion. Hence, no mechanisms could be identified that are involved in the transmission of maltreatment. Hypersensitivity to social rejection by strangers in neglected individuals underscores the importance to distinguish between effects of abuse and neglect and suggests that the impact of experiencing rejection and maltreatment by your own parents extends beyond the family context.

Keywords: social rejection, child maltreatment, insula, ACC, dmPFC

INTRODUCTION

Child physical and emotional abuse and neglect are associated with increased risk for long-lasting behavioral, physical and mental health problems (e.g. Heim *et al.*, 2010; Spinhoven *et al.*, 2010; Twardosz and Lutzker, 2010; McCrory *et al.*, 2011a; Norman *et al.*, 2012; Spinhoven *et al.*, 2014). Among the adverse consequences is the increased risk for maltreated individuals to maltreat their own children (e.g. Kaufman and Zigler, 1987; Egeland *et al.*, 1988; Pears and Capaldi, 2001; Dixon *et al.*, 2005; Berlin *et al.*, 2011). To better identify risk factors for perpetrating abuse and neglect, it is crucial to examine factors that might play a role in the transmission of maltreatment. In this multigenerational family study, we aim to investigate the impact of experienced and perpetrated abuse and neglect on neural reactivity to social exclusion in 144 family members (90 parents and 54 offspring). The possible role of sensitivity to social rejection in the intergenerational transmission of maltreatment is also examined.

One of the core aspects of both child abuse and neglect is parental rejection of needs for attention and nurturance (Bolger and Patterson, 2001; Glaser, 2002), which can occur through parental aggression and hostility or via parental neglect and indifference (Loue, 2005). Chronic exposure to rejection during childhood is associated with emotional, cognitive, behavioral and social deficits, for instance, decreased self-esteem and hypersensitivity to signs of threat and rejection (Van Beest and Williams, 2006; DeWall and Bushman, 2011; Eisenberger, 2012; Sreekrishnan *et al.*, 2014). Rejection sensitivity is associated with increased feelings of aggression and aggressive behavior (Downey and Feldman, 1996; Downey *et al.*, 1998; Jacobs and Harper, 2013). Being rejected by your own parents can enhance sensitivity for social rejection in all sorts of situations, including next-generation parent-child interactions.

Multiple studies show that the network of brain areas associated with social rejection and exclusion includes the insula, anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC; e.g. Eisenberger *et al.*, 2003; DeWall *et al.*, 2010; Bolling *et al.*, 2011; Sebastian *et al.*, 2011; Cacioppo *et al.*, 2013; Eisenberger, 2015; Rotge *et al.*, 2015;). The insula and ACC are key brain regions involved in social functioning (Wager and Barrett, 2004; Shackman *et al.*, 2011; Cacioppo *et al.*, 2012, 2013), including empathic abilities (Carr *et al.*, 2003; Lamm *et al.*, 2007; Shirtcliff *et al.*, 2009; Rameson *et al.*, 2012). The mPFC is implicated in self-processing, cognitive control, social evaluation and regulation of stress and negative emotions (Ochsner and Gross, 2005; Güroğlu *et al.*, 2010; Etkin *et al.*, 2011; Sebastian *et al.*, 2011; Van den Bos *et al.*, 2011; Denny *et al.*, 2012).

Altered neural responses to social exclusion (compared to social inclusion) have been observed in maltreated individuals. For instance, children with early separation experiences showed reduced activation in the dorsal ACC (dACC) and dorsolateral PFC (dlPFC) and reduced dlPFC–dACC connectivity (Puetz *et al.*, 2014). Maltreated children

also showed a hypoactivation to rejection-related words, including the left anterior insula and ventrolateral PFC (vlPFC; Puetz *et al.*, 2016). In young adults, in contrast, childhood emotional maltreatment (CEM) severity was found to be associated with increased dorsal mPFC (dmPFC) responsivity to social exclusion, suggesting they show increased levels of self- and other referential processing after social exclusion (Van Harmelen *et al.*, 2014).

A history of maltreatment appears to affect neural networks (i.e. insula, ACC and mPFC) that are also implicated in parenting behavior (Swain and Ho, 2017). These networks enable parents to respond to infant pain and emotions, understand non-verbal signals and infer intentions through empathy and mentalizing (Feldman, 2015; Rilling and Mascaro, 2017). Neural alterations in these areas implicated in social exclusion might mediate the association between experienced and perpetrated abuse and neglect. The current study is the first to examine the role of the neural correlates of social exclusion in the transmission of maltreatment.

Individual differences in response to social exclusion may depend on the relationship with the person who is excluding (Krill and Platek, 2009; Bernstein *et al.*, 2010; Sacco *et al.*, 2014; Scanlon, 2015). Since child maltreatment takes place within the family context, an important question is whether maltreated individuals display a general rejection sensitivity or a more specific hypervigilance for exclusion in their own parent–child context. No functional magnetic resonance imaging (fMRI) studies have been conducted comparing responsivity to exclusion by family members versus strangers. An electroencephalogram (EEG) study suggested however increased sensitivity to exclusion by family members as reflected by increased frontal P2 peaks and left frontal positive slow waves in mothers and children when excluded by one another versus by a stranger (Sreekrishnan *et al.*, 2014). The current study is the first that aims to unravel the neural activity following exclusion by one's own mother or child versus strangers and how this is specifically affected in maltreated and maltreating individuals.

In sum, this study examined the impact of experienced and perpetrated abuse and neglect on neural reactivity to social exclusion by strangers and family members. We used a multi-informant, multigenerational family design, including 144 participants from 8 to 69 years. We differentiated between effects of (experienced and perpetrated) abuse and neglect, as abuse and neglect may be differentially related to the affective and neural correlates of social rejection (e.g. Compier-de Block *et al.*, 2016; Nemeroff, 2016; Van den Berg *et al.*, 2017). We predicted that experienced and perpetrated child abuse and neglect are associated with altered sensitivity to social signals and rejection as reflected by decreased ACC, insular and/or increased dmPFC responsivity to social exclusion. As a second aim, we examined whether the effects represent a general sensitivity to exclusion or a specific sensitivity to one's own family members.

MATERIALS AND METHODS

Participants

The current sample was part of a larger sample from the 3G parenting study, a three-generation family study on the intergenerational transmission of parenting styles, stress and emotion regulation (see also Compier-de Block, 2017; Van den Berg *et al.*, 2017). Participants were recruited via three other studies that included the assessment of caregiving experiences (Penninx *et al.*, 2008; Scherpenzeel, 2011; Joosen *et al.*, 2013). We oversampled participants with an increased risk of maltreatment and included participants who had at least one child of 8 years or older. After consent for participation in the 3G study, their family members (parents, partners, offspring, adult siblings, nephews, nieces and in-laws) were invited to participate. For the current study, all participants from the 3G study who participated in the fMRI part of the study were included. In total, we included 144 participants from two generations (parents and their offspring) of 54 families.

Participants played one round of the Cyberball task with strangers and one with family. We included only the first round of Cyberball in our analyses (using a between-subject design) because affective and neural effects of exclusion were only observed in the first round of the task, irrespective of the familiarity of the other players. This was possibly due to habituation to the task. Participants played their first round of Cyberball with strangers (unfamiliar condition; 28 men and 44 women) or with family (familiar condition; $n = 72$; see Figure 1). In the familiar condition, 41 participants played with their child (18 men and 23 women) and 31 with their mother (11 men and 20 women). Separate analyses were run to link experienced maltreatment (all participants; $n = 144$) and perpetrated maltreatment (parents only; $n = 90$) to neural responses. See Supplementary data for more information.

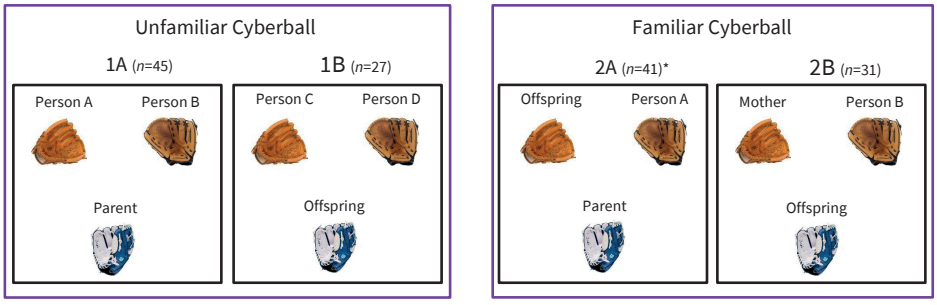


Figure 1. Unfamiliar (1A and 1B) and familiar (2A and 2B) Cyberball for parents (1A and 2A) and offspring (1B and 2B). *Four parents played with their mother because their offspring were too young to participate.

Procedure

Informed consent was obtained after describing the study to the participants. If eligible, offspring and their parents were asked to participate in the fMRI session, performing three tasks in the scanner, with the Cyberball task always second. Results on the other tasks are reported elsewhere (Van den Berg *et al.*, 2017). All participants younger than 18 years old were first familiarized with the scanner environment using a mock scanner. The full protocol was conducted according to the principles expressed in the Declaration of Helsinki and approved by the Medical Ethics Committee of the Leiden University Medical Center (LUMC).

Measures

Childhood maltreatment

Adapted versions of the Conflict Tactics Scales (CTS; Straus *et al.*, 1998) were administered in combination with the emotional neglect scale from the Childhood Trauma Questionnaire (CTQ-SF; Bernstein *et al.*, 2003; see also Compier-de Block, 2017) to measure experienced childhood abuse and neglect by mother and/or father. Parents also completed a CTS version to assess their own abusive or neglectful behaviors towards their child(ren). An overall *Neglect* score was calculated by averaging Emotional and Physical Neglect and an overall *Abuse*-score by averaging Emotional and Physical Abuse. For our analyses, we combined information from two informants (parents and offspring) whenever possible (see Supplementary data), resulting in a total of 237 informants on experienced childhood maltreatment and 163 informants on perpetrated maltreatment. Because the distributions of CTS scores were skewed, scores were logarithmically transformed (log10). Outliers, meaning values more extreme than a standardized value of ±3.29, were winsorized to the most extreme value within the normal range ± the difference between the two most extreme values within the normal range (n = 1 for experienced abuse and n = 1 for neglect).

Cyberball task

The Cyberball task is a commonly used paradigm to study the neural correlates of social exclusion (Williams *et al.*, 2000). For the current study, an adapted version of the task was used in which participants played two rounds of this virtual ball-tossing game with two other players (computer controlled confederates; see Supplementary data). All participants played one round with two strangers (unfamiliar round) and another round with a family member and a stranger (familiar round). For offspring, this family member was their own mother, and parents played with their oldest child (participating in the 3G study). The order of the rounds was counterbalanced across participants within the two generations. As described above, only the first round of Cyberball was included in our analyses. During the game, each player was represented by a picture of a different baseball glove (see Figure 1).

Each round consisted of an inclusion and exclusion block of 36 trials each. During the inclusion block, the ball was thrown to the participant in 33% of the total number of tosses (hence, achieving fair play in which the participant got an equal number of tosses as compared to the other players). After receiving the ball, participants could throw back the ball to one of the other players using a button press. The inclusion block was followed by a social exclusion block with the same players, during which participants received the ball only once at the start of the game (the unfair play in which participants were excluded from the game). Participants' tosses were self-paced, and ball tosses of the other players were preceded by a random jitter interval (100–4000 ms). It took 2 s before each toss reached the designated player, and ball tosses varied in trajectory. The task was projected on a screen at the end of the scanner and was visible via a mirror positioned on the head coil.

Mood and need satisfaction

Right before the Cyberball game (inside the scanner) and immediately after each round of the game, participants completed four items from a mood questionnaire (Sebastian *et al.*, 2010). The items measured feeling sad, happy, angry and insecure. After each Cyberball round, additional items from the Need Threat Scale (Van Beest and Williams, 2006) were completed to measure levels of need satisfaction. The five items from the Need Threat Scale measured belonging, control, self-esteem and meaningful existence. All questions were presented on the screen. Each item was rated on a scale from 1 ('not at all') to 10 ('very much'). Items were recoded and averaged to create an overall index of mood and need satisfaction at each time point with higher scores reflecting a better mood (see Table 1) and higher levels of need satisfaction.

Table 1. Mood (SD) before the Cyberball, after round 1 for parents and offspring.

	Parents	Offspring
Baseline	8.39 (1.04)	8.80 (0.86)
After round 1 of Cyberball	8.16 (1.23)**	8.55 (1.15)*

* $p < .05$; ** $p < .01$ compared to baseline

Covariates

Questionnaires were used to assess demographic information (age, gender, handedness and household social economic status [SES]). Three versions of Achenbach's behavior problems assessment were used to control for psychopathology symptoms. Parents completed the Child Behavioral Checklist (CBCL; Achenbach, 1991a) when their child was younger than 12 years old. For 12- to 17-year-old participants, the Youth Self Report (YSR; Achenbach, 1991b; Achenbach and Rescorla, 2001) was used, and older participants completed the Adult Self Report (ASR; Achenbach and Rescorla, 2003). A total psychopa-

thology symptom score was calculated for all three questionnaires. Cronbach's α's were good to excellent (.76–.93).

fMRI acquisition

Imaging data were acquired using a whole-head coil on a 3.0-Tesla Philips Achieva scanner (Philips Medical Systems, Best, the Netherlands) located at the LUMC. To restrict head motion, foam cushions were used around the head. T2*-weighted echo-planar images (EPI) were obtained for all participants [repetition time (TR) = 2200 ms, echo time (TE) = 30 ms, matrix size: 80 × 79, 38 transverse slices of 2.75 mm, slice gap = 0.28 mm, field of view (FOV) = 220]. In accordance with the LUMC policy, all anatomical MRI scans were reviewed and cleared by a radiologist from the radiology department. No anomalous findings were reported.

fMRI data analysis

Functional imaging data were preprocessed and analyzed using Statistical Parametric Mapping version 8 (SPM8; Wellcome Department of Cognitive Neurology, London) software implemented in Matlab 5.0.7 (Mathworks, Sherborn, MA). Preprocessing, after extensive quality control of the data, included manually reorienting the functional images to the anterior commissure, slice time correction, image realignment, registration of the T1-scan to the mean echo-planar image, warping to Montreal Neurological Institute (MNI)-space as defined by the SPM8 T1-template, reslicing to 3 × 3 × 3 mm voxels and spatial smoothing with a Gaussian kernel (8 mm, full width at half-maximum). Subject movement (>3 mm) resulted in exclusion of the data from further analysis (n = 16).

MRI data were analyzed with the General Linear Model in SPM8. The fMRI time series were modeled as a series of events convolved with the hemodynamic response function (HRF). BOLD responses were distinguished for events on which participants received or did not receive the ball by a stranger or a family member (see Supplementary data). The first trials of the exclusion blocks during which participants received and played the ball once were not analyzed. The onset of the ball movement was modeled as a zero-duration event. Low-frequency noise was removed by applying a high-pass filter (cut-off 120 s) to the fMRI time series at each voxel. Statistical parametric maps for each comparison of interest were calculated on a voxel-by-voxel basis.

To examine the effect of social exclusion, the following contrasts were computed for all participants for the familiar and unfamiliar round: no-ball exclusion block > no-ball inclusion block. To test neural correlates of social exclusion, key region of interests (ROIs) were identified using the MARSBAR toolbox (Brett *et al.*, 2002) in SPM: namely, the insula, dACC and dmPFC (see Figure 2). We defined anatomical ROIs of the insula using the TD label atlas within the Wakeforest-pickatlas toolbox (Maldjian *et al.*, 2003). Because the boundaries of ACC subdivisions are to date not well defined (Lieberman and Eisenberger,

2015; Rotge *et al.*, 2015), and the whole brain peak voxels of the ACC were located in different areas of the ACC dependent on whether participants were playing with strangers or family members (see Figure 2), we extracted two distinct areas of the dACC as functional ROIs (Poldrack, 2007) using the MARSBAR toolbox (Brett *et al.*, 2002). We generated the dACC functional ROIs using whole-brain activation of the unfamiliar round to analyze the no-ball exclusion block versus no-ball inclusion block contrast for the unfamiliar condition and whole brain activation of the familiar round for the familiar condition (see Figure 2, Tables 2 and 3). Additionally, because CEM was found to be specifically associated with enhanced dmPFC activity to social exclusion (Van Harmelen *et al.*, 2014), this area was defined by a 10-mm sphere around the peak activation described by Van Harmelen *et al.* (2014; centered on MNI-coordinates x = −3, y = 48, z = 33). All results are reported in MNI space.

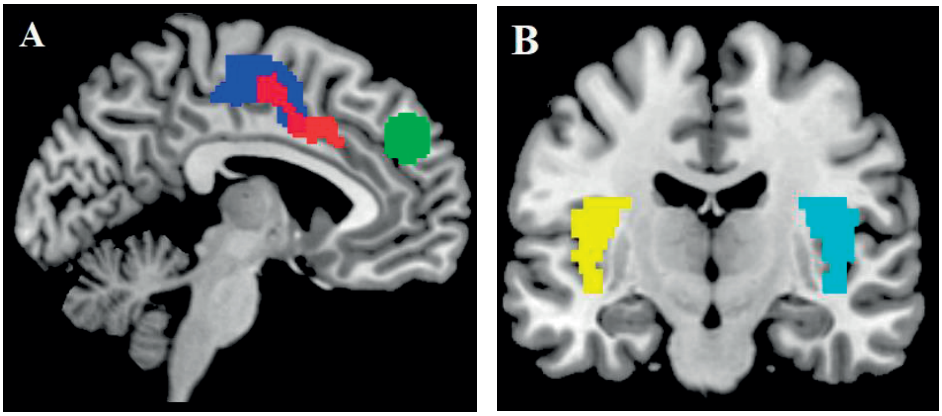


Figure 2. Region of interest (ROI) masks.
A = Red: functional ACC ROI mask for the unfamiliar condition based on whole brain activation for the contrast no-ball exclusion>no-ball inclusion at $p < 0.005$ (uncorrected); Dark blue: functional ACC ROI mask for the familiar condition based on whole brain activation for the contrast no-ball exclusion>no-ball inclusion at $p < 0.005$ (uncorrected); Green: dmPFC ROI mask based on the peak activation described by Van Harmelen et al. (2014; centered on MNI-coordinates x=-3, y=48, z=33).
B = Yellow: anatomical left insula ROI mask; Cyan: anatomical right insula ROI mask.

SPSS data analysis

Activity in the ROIs was examined using three-level multilevel regression analyses in SPSS 23, in which participants were nested within households and households were nested within families, to take the family structure of the data into account. This way, level 1 models variation at the participant level, level 2 captures variation among participants within the same households and level 3 estimates variation among families. Random intercept models were built sequentially, starting with an empty (null) model without explanatory variables in which the total variance in brain reactivity in response to social exclusion was

divided into a component at each level. This empty model was used to test for random variation in the outcome variables at the different levels (see Supplementary data). We consistently used multilevel analyses for all ROIs to control for the nested structure of data.

As a next step, age, gender, handedness, SES and psychopathology were added to the model as possible covariates. Variables were only kept in the final covariates model when they were significant ($p < 0.05$). To explore fixed effects of abuse and neglect, main effects of abuse and neglect were added to Model 1.

Multilevel regression analyses were run for each ROI for the familiar and the unfamiliar contrast separately. Separate models were run for experienced and perpetrated maltreatment. For multilevel analyses in the context of the familiar Cyberball, participants playing with their own child (41 parents) or mother (31 offspring) were analyzed separately (see Figure 1). All (continuous) predictor variables and covariates were centered. All independent and dependent variables were measured at the individual level (except SES; see Supplementary data) and considered in the fixed part of the model. Unstandardized regression coefficients are reported. If similar significant ROIs were found for experienced and perpetrated abuse and/or neglect, mediation analyses were planned to assess their role in the intergenerational transmission of maltreatment. However, this was not relevant for the current findings.

Table 2. Significant clusters for the contrast no-ball exclusion block > no-ball inclusion block for the unfamiliar Cyberball round.

Clusters	Cluster level	Peak level		Coordinates		
	number of voxels	T	*p*-value	x	y	z
Left insula	832	5.74	<0.001	-33	8	7
		5.44	<0.001	-24	-4	1
		5.35	<0.001	-45	-7	13
Precentral gyrus		3.69	<0.001	-57	5	10
Postcentral gyrus	169	4.99	<0.001	48	-22	25
ACC	269	4.90	<0.001	-6	11	37
		3.85	<0.001	0	-7	55
		3.51	<0.001	9	5	43
Right insula	450	4.21	<0.001	45	2	4
		4.04	<0.001	36	-1	13
		3.91	<0.001	54	5	4

$p < 0.005$ uncorrected, > 25 voxels

Table 3. Significant clusters for the contrast no-ball exclusion block>no-ball inclusion block for the familiar Cyberball round for parents (A) and offspring (B).

A. Parents (*n* = 90)						
Clusters	Cluster level	Peak level		Coordinates		
	number of voxels	T	*p*-value	x	y	z
Postcentral gyrus	62	4.68	<0.001	-54	-25	43
		4.47	<0.001	-45	-28	49
Precentral gyrus		4.16	<0.001	-33	-25	55
ACC	152	4.57	<0.001	6	-7	52
		3.91	<0.001	-9	-7	52
		3.77	<0.001	-12	-31	49
Precentral gyrus	34	3.68	<0.001	33	-25	52

p < 0.005 uncorrected, > 25 voxels

B. Offspring (*n* = 54)						
Clusters	Cluster level	Peak level		Coordinates		
	number of voxels	T	*p*-value	x	y	z
ACC	567	6.34	<0.001	-6	-4	55
		6.00	<0.001	6	2	52
		5.44	<0.001	-6	5	43
Left insula	165	5.35	<0.001	-42	-4	10
Precentral gyrus	185	5.00	<0.001	36	-22	55
		4.11	<0.001	42	-19	67
		3.71	<0.001	42	-28	67
Postcentral gyrus	230	4.93	<0.001	-54	-19	49
		4.46	<0.001	-45	-22	55
		3.86	<0.001	-36	-28	52
Right insula	65	3.85	<0.001	42	-25	22
Postcentral gyrus		3.46	0.001	54	-19	22
		3.43	0.001	60	-25	25
Left insula	72	3.77	<0.001	-45	-22	19
Postcentral gyrus		3.77	<0.001	-63	-22	31
		3.29	0.001	-57	-22	22

p < 0.005 uncorrected, > 25 voxels

RESULTS

Transmission of maltreatment

Demographics and mean (SD) maltreatment scores are presented in Table 4. The correlation between experienced abuse and neglect was $r = .51$ ($p < 0.001$) and between perpetrated abuse and neglect $r = .34$ ($p = 0.001$). To examine intergenerational transmission of maltreatment in our sample, regression analyses were conducted with experienced childhood abuse and neglect as predictors and with perpetrated abuse and neglect as outcome measures separately for participants with offspring ($n = 88$ parents). Results indicated that, controlling for age, gender, household SES and psychopathology in the first block, experienced abuse ($\beta = .53$, $t(81) = 4.66$, $p < 0.001$) was the only significant predictor of perpetrated abuse. Experienced neglect did not predict perpetrated abuse ($p = 0.113$). None of the covariates were significant. Perpetrated neglect was not predicted by experienced neglect ($p = 0.306$) nor by experienced abuse ($p = 0.945$). Age ($\beta = 0.29$, $t = 2.54$, $p = .013$) and psychopathology ($\beta = 0.30$, $t = 2.68$, $p = .009$) were significant covariates for perpetrated neglect.

Table 4. Demographics, psychopathology, and maltreatment scores.

Variables	Mean (SD)	Range
Age	36.85 (16.38)	8.75 - 69.67
Gender (*n:* men/women)	57/87	-
Handedness (*n*: left/right)	18/126	-
CBCL	14.00 (7.64)	3.20 - 28.80
YSR	9.68 (8.27)	0.00 - 30.00
ASR	24.22 (15.69)	1.00 - 83.00
Abused[a]	1.65 (0.50)	1.02 - 4.50
Neglected[a]	1.89 (0.61)	1.00 - 5.00
Maltreated[a] (total)	1.77 (0.49)	1.02 - 4.75
Abusive[b] ($n = 90$)	1.49 (0.31)	1.00 - 2.53
Neglectful[b] ($n = 90$)	1.55 (0.32)	1.00 - 2.48
Maltreating[b] (total; $n = 90$)	1.52 (0.25)	1.00 - 2.11

Values of all included participants are presented ($n = 144$) unless otherwise specified.
Raw scores are presented.
[a]Combined experienced maltreatment scores by averaging parent and child reports as measured with the CTS. [b]Combined perpetrated maltreatment scores by averaging parent and child reports as measured with the CTS.
CBCL = Child Behavioral Checklist; YSR = Youth Self Report; ASR = Adult Self Report.

Mood and need satisfaction

A time (mood before versus after the first round of Cyberball) × type (playing with family or strangers) repeated measures ANOVA with mood as a dependent variable showed a significant main effect of time on mood for parents ($F(1, 80) = 8.76$, $p = 0.004$) and offspring ($F(1, 60) = 6.10$, $p = 0.016$), with mood scores significantly decreasing after the first Cyberball round compared to baseline for both parents and offspring. There were no significant interaction effects between time and type for parents ($p = 0.097$) or offspring ($p = 0.260$).

Correlation analyses revealed that levels of experienced or perpetrated abuse or neglect were not related to mood after exclusion during the Cyberball task for parents ($p > 0.05$). However, a lower mood after exclusion was significantly related with higher levels of experienced abuse ($r = -.37$, $p = 0.003$) and neglect ($r = -.38$, $p = 0.003$) for children. No relationships were found between experienced or perpetrated abuse or neglect and need satisfaction after the Cyberball task for parents or children ($p > 0.05$).

Unfamiliar Cyberball

Whole brain analyses

For the unfamiliar Cyberball ($n = 72$; see Figure 1), whole brain analyses for the contrast no-ball exclusion block versus no-ball inclusion block revealed a significant cluster of activation in the left insula at $p < 0.01$ family-wise error (FWE) corrected for multiple comparisons. For exploratory purposes, brain activation was also examined at the whole brain level with a threshold of $p < 0.005$ (uncorrected). To reduce the risk of false positives, only clusters larger than 25 significantly activated voxels were considered (Lieberman and Cunningham, 2009). At this threshold, the contrast no-ball exclusion block versus no-ball inclusion block showed activation in clusters including the insula and ACC (see Table 2).

Multilevel ROI analyses: experienced abuse and neglect

Multilevel analyses were first performed for the contrast no-ball exclusion by strangers versus no-ball inclusion by strangers for all participants in the unfamiliar Cyberball condition ($n = 72$; see Figure 1). Analyses were run with experienced abuse and neglect as predictors and BOLD responses in the ROIs as outcome measures (see Tables 5A-8A and Supplementary data). In none of these multilevel analyses age, gender, handedness, SES nor psychopathology were significant covariates.

Adding abuse and neglect experience as predictors significantly improved the models for activation in the left (χ^2 (2) = 8.75, $p = 0.013$) and right insula (χ^2 (2) = 6.07, $p = 0.048$), dACC (χ^2 (2) = 8.70, $p = 0.013$) and dmPFC (χ^2 (2) = 11.09, $p = 0.004$). Higher levels of experienced maltreatment were associated with higher BOLD responses in the left and right insula and the dmPFC, and with lower BOLD responses in the dACC during social exclusion by strangers. Analyses on experienced abuse versus neglect revealed that the increased

Table 5A. Multilevel model of brain reactivity in the left insula in response to social exclusion as related to experienced and perpetrated abuse and neglect: unfamiliar Cyberball

Left insula: Unfamiliar round							
	Experienced maltreatment				Maltreating behavior		
	Parents and offspring (n = 72)				*Parents (n = 45)*		
	b	SE	*p*		*b*	SE	*p*
abused	0.28	1.68	.869	abusive	3.01	2.12	.162
neglected	2.31	1.65	.167	neglectful	-2.86	2.38	.236
	χ^2 (2) = 8.75*		.013		χ^2 (2) = 2.34		.311

* $p < .05$; ** $p < .01$
Significant covariates are included in the model (see Supplement)
SE = standard deviation

Table 5B. Multilevel model of brain reactivity in the left insula in response to social exclusion as related to experienced and perpetrated abuse and neglect: familiar Cyberball

Left insula: Familiar round									
	Experienced maltreatment						Maltreating behavior		
	Parents (n = 41)			*Offspring (n = 31)*			*Parents (n = 41)*		
	b	SE	*p*	*b*	SE	*p*	*b*	SE	*p*
abused	0.70	1.12	.538	3.42	2.65	.207	abusive	0.62	1.75	.724
neglected	-0.34	1.02	.740	-0.56	2.67	.836	neglectful	-0.22	1.27	.861
	χ^2 (2) = 0.40		.817	χ^2 (2) = 1.65		.437		χ^2 (2) = 0.12		.941

* $p < .05$; ** $p < .01$
Significant covariates are included in the model (see Supplement)
SE = standard deviation

reactivity in the left insula (β = 2.49, t = 2.03, p = 0.046) and dmPFC (β = 3.27, t = 2.07, p = 0.042) were mainly due to neglect.

Multilevel ROI analyses: perpetrated abuse and neglect

Similar multilevel analyses were run for parents in the unfamiliar Cyberball condition (n = 45; see Figure 1) with perpetrated abuse and neglect as predictors for the contrast no-ball exclusion by strangers versus no-ball inclusion by strangers (see Tables 5A-8A and Supplementary data). Age, gender, handedness, SES and psychopathology were not significant as covariates in any of those analyses.

Adding perpetrated abuse and neglect as predictors did not significantly improve the models for activation in the left (χ^2 (2) = 2.34, p = 0.311) or right insula (χ^2 (2) = 4.27, p = 0.119), dACC (χ^2 (2) = 2.80, p = 0.247) or dmPFC (χ^2 (2) = 2.39, p = 0.302) regarding exclusion by strangers.

Table 6A. Multilevel model of brain reactivity in the right insula in response to social exclusion as related to experienced and perpetrated abuse and neglect: unfamiliar Cyberball

Right insula: Unfamiliar round								
	Experienced maltreatment					Maltreating behavior		
	Parents and offspring (n = 72)					*Parents (n = 45)*		
	b	SE	*p*			*b*	SE	*p*
abused	-0.17	1.77	.922		abusive	0.78	2.20	.725
neglected	1.13	1.73	.516		neglectful	-5.17*	2.46	.041
	χ^2 (2) = 6.07*		.048			χ^2 (2) = 4.27		.119

* $p < .05$; ** $p < .01$
Significant covariates are included in the model (see Supplement)
SE = standard deviation

Table 6B. Multilevel model of brain reactivity in the right insula in response to social exclusion as related to experienced and perpetrated abuse and neglect: familiar Cyberball

Right insula: Familiar round										
	Experienced maltreatment							Maltreating behavior		
	Parents (n = 41)			*Offspring (n = 31)*				*Parents (n = 41)*		
	b	SE	*p*	*b*	SE	*p*		*b*	SE	*p*
abused	0.58	.74	.454	3.51	2.91	.237	abusive	0.71	1.57	.656
neglected	-0.16	1.02	.877	0.87	2.96	.770	neglectful	-0.41	1.03	.699
	χ^2 (2) = 0.59		.746	χ^2 (2) = 1.68		.432		χ^2 (2) = 0.20		.904

* $p < .05$; ** $p < .01$
Significant covariates are included in the model (see Supplement)
SE = standard deviation

Familiar Cyberball

Whole brain analyses

For the familiar Cyberball ($n = 72$; see Figure 1), whole brain analyses for the contrast no-ball exclusion block versus no-ball inclusion block showed a significant cluster of activation in the ACC at $p < 0.01$ FWE corrected for multiple comparisons. At $p < 0.005$ (uncorrected, 25 voxels) both parents and offspring showed activation in clusters including the ACC during exclusion (see Table 3 for an overview of all activated clusters). Moreover, offspring also showed activation in the left and right insula during exclusion by their parents, whereas this was not found for parents playing with their offspring.

Multilevel ROI analyses: experienced abuse and neglect

Multilevel analyses were repeated for the contrast no-ball exclusion by family versus no-ball inclusion by family for participants in the familiar Cyberball condition for parents ($n = 41$) and offspring ($n = 31$) separately (see Figure 1, Tables 5B–8B and Supplementary data).

Table 7A. Multilevel model of brain reactivity in the dACC in response to social exclusion as related to experienced and perpetrated abuse and neglect: unfamiliar Cyberball

dACC: Unfamiliar round							
	Experienced maltreatment				Maltreating behavior		
	Parents and offspring (n = 72)				*Parents (n = 45)*		
	b	SE	*p*		*b*	SE	*p*
abused	-2.72	2.12	.206	abusive	-4.59	2.70	.096
neglected	2.61	2.05	.207	neglectful	1.34	3.03	.660
	χ^2 (2) = 8.70*		.013		χ^2 (2) = 2.80		.247

* $p < .05$; ** $p < .01$
Significant covariates are included in the model (see Supplement)
SE = standard deviation

Table 7B. Multilevel model of brain reactivity in the dACC in response to social exclusion as related to experienced and perpetrated abuse and neglect: familiar Cyberball

dACC: Familiar round										
	Experienced maltreatment							Maltreating behavior		
	Parents (n = 41)			*Offspring (n = 31)*				*Parents (n = 41)*		
	b	SE	*p*	*b*	SE	*p*		*b*	SE	*p*
abused	1.04	1.52	.497	1.36	2.47	.586	abusive	-0.84	2.03	.683
neglected	-0.28	1.34	.836	-0.80	2.43	.745	neglectful	0.73	2.05	.725
	χ^2 (2) = 0.47		.792	χ^2 (2) = 0.32		.851		χ^2 (2) = 0.20		.903

* $p < .05$; ** $p < .01$
Significant covariates are included in the model (see Supplement)
SE = standard deviation

Parents

For parents, a higher SES was associated with higher activity in the left ($\beta = 0.37$, $t = 2.09$, $p = 0.043$) and right insula ($\beta = 0.43$, $t = 2.41$, $p = 0.021$). Higher levels of psychopathology were associated with higher right insula activation ($\beta = 1.71$, $t = 3.41$, $p = 0.006$). Age, gender and handedness were not significant covariates in those analyses.

Adding experiences of abuse and neglect as predictors did not significantly improve the models for activation in the left (χ^2 (2) = 0.40, $p = 0.817$) or right insula (χ^2 (2) = 0.59, $p = 0.746$), dACC (χ^2 (2) = 0.47, $p = 0.792$) or dmPFC (χ^2 (2) = 3.91, $p = 0.142$) regarding exclusion by offspring.

Offspring

For offspring, higher levels of psychopathology were associated with higher activity in the right insula ($\beta = 3.10$, $t = 2.60$, $p = 0.013$). Right-handed participants exhibited higher dACC activation ($\beta = -1.68$, $t = -2.61$, $p = 0.014$). Age, gender and SES were not significant covariates in any of those analyses.

Table 8A. Multilevel model of brain reactivity in the dmPFC in response to social exclusion as related to experienced and perpetrated abuse and neglect: unfamiliar Cyberball

dmPFC: Unfamiliar round								
	Experienced maltreatment					Maltreating behavior		
	Parents and offspring (n = 72)					*Parents (n = 45)*		
	b	SE	*p*			*b*	SE	*p*
abused	1.17	2.16	.591		abusive	4.12	2.82	.151
neglected	2.50	2.12	.242		neglectful	-3.03	3.16	.343
	χ^2 (2) = 11.09**		.004			χ^2 (2) = 2.39		.302

* $p < .05$; ** $p < .01$
Significant covariates are included in the model (see Supplement)
SE = standard deviation

Table 8B. Multilevel model of brain reactivity in the dmPFC in response to social exclusion as related to experienced and perpetrated abuse and neglect: familiar Cyberball

dmPFC: Familiar round										
	Experienced maltreatment							Maltreating behavior		
	Parents (n = 41)			*Offspring (n = 31)*				*Parents (n = 41)*		
	b	SE	*p*	*b*	SE	*p*		*b*	SE	*p*
abused	0.82	1.75	.640	-2.19	2.71	.426	abusive	-2.08	2.43	.396
neglected	-3.26*	1.52	.038	1.36	2.68	.616	neglectful	1.83	2.13	.396
	χ^2 (2) = 3.91		.142	χ^2 (2) = 0.69		.707		χ^2 (2) = 0.997		.607

* $p < .05$; ** $p < .01$
Significant covariates are included in the model (see Supplement)
SE = standard deviation

Adding experiences of abuse and neglect as predictors did not significantly improve the models for activation in the left (χ^2 (2) = 1.65, $p = 0.437$) or right insula (χ^2 (2) = 1.68, $p = 0.432$), dACC (χ^2 (2) = 0.32, $p = 0.851$) or dmPFC (χ^2 (2) = 0.69, $p = 0.707$) regarding exclusion by parents for offspring.

Multilevel ROI analyses: perpetrated abuse and neglect

Multilevel analyses were repeated for the contrast no-ball exclusion by family versus no-ball inclusion by family for all parents in the familiar Cyberball condition ($n = 41$; see Figure 1, Tables 5B–8B and Supplementary data). Younger participants ($\beta = -0.03$, $t = -3.54$, $p = 0.003$) and participants with higher levels of psychopathology ($\beta = 1.50$, $t = 3.42$, $p = 0.004$) exhibited higher activity in the right insula. Gender was a significant covariate for the dACC ($\beta = 0.64$, $t = 2.09$, $p = 0.044$; higher activation in men). Handedness and SES were not significant.

Adding perpetrated abuse and neglect as predictors did not significantly improve the models for activation in the left (χ^2 (2) = 0.12, $p = 0.941$) or right insula (χ^2 (2) = 0.20, $p =$

0.904), dACC (χ^2 (2) = 0.20, p = 0.903) or dmPFC (χ^2 (2) = 0.997, p = 0.607) in the context of exclusion by family.

DISCUSSION

This is the first multigenerational family study that examined the impact of experienced and perpetrated abuse and neglect on neural reactivity to social exclusion. Moreover, we examined whether the effects represented a general sensitivity to exclusion or a sensitivity in the family context. Previous neuroimaging studies showed that being excluded during the Cyberball task in the general population is typically associated with activation in the insula, ACC and mPFC (e.g. Eisenberger *et al.*, 2003; DeWall *et al.*, 2010; Sebastian *et al.*, 2011; Bolling *et al.*, 2011; Cacioppo *et al.*, 2013; Eisenberger, 2015; Rotge *et al.*, 2015). We also found that social exclusion was associated with insular and ACC activation. However, our whole brain analyses revealed differential reactivity to social exclusion by strangers versus family (one's own mother or child). That is, exclusion by strangers was significantly associated with increased BOLD responses in the left insula, while exclusion by a family member was mainly associated with increased activation in the ACC, especially in offspring.

There are no previous fMRI studies comparing neural responsivity to exclusion by family members versus strangers. However, an EEG study found increased responses in mothers and their offspring while they were excluded by one another compared to a stranger (Sreekrishnan *et al.*, 2014). The insula and ACC are both involved in social functioning (Wager and Barrett, 2004; Shackman *et al.*, 2011; Cacioppo *et al.*, 2012, 2013), including empathic abilities (Carr *et al.*, 2003; Lamm *et al.*, 2007; Shirtcliff *et al.*, 2009; Rameson *et al.*, 2012). However, the insula is found to be involved in automatic affective–empathic processing, whereas the ACC is associated with more general cognitive functions, for instance, task control and response selection (Gu *et al.*, 2010) but also with the motivational component of emotions (Craig, 2009). ACC activity is also found in response to viewing a loved one, for example a child (Bartels and Zeki, 2004).

Experienced abuse and neglect

Exclusion by strangers

As expected, maltreated individuals showed altered neural responses to social exclusion by strangers. Maltreated offspring and parents showed higher activity in the left and right insula and the dmPFC and lower reactivity in the dACC during social exclusion by strangers. Higher activity in the left insula and dmPFC during social exclusion by strangers was especially associated with experienced neglect. Increased dmPFC responsivity to social exclusion by strangers in neglected individuals is in line with previous findings for individu-

als who experienced CEM (Van Harmelen *et al.*, 2014), strengthening the hypothesis that neglected individuals show increased levels of self- and other-referential processing after social exclusion (e.g., Gusnard *et al.*, 2001; Kelley *et al.*, 2002; Mitchell *et al.*, 2005). Lower dACC reactivity in maltreated individuals is also in line with reduced dACC activation during social exclusion in children with early separation experiences (Puetz *et al.*, 2014) and might reflect avoidant or dissociative responses (Krause-Utz *et al.*, 2012; Herringa *et al.*, 2013; Puetz *et al.*, 2016).

Higher insula activity during social exclusion by strangers in maltreated individuals is consistent with increased insular activity in response to angry faces and trauma-related words in maltreated children (McCrory *et al.*, 2011b; Thomaes *et al.*, 2012) but is not in line with a blunted insula response to rejection-related words in maltreated children (Puetz *et al.*, 2016). Since the insula is associated with various functions including self-awareness and emotion processing (Phan *et al.*, 2002), altered insula activation seems to be linked to functional deficits in emotion processing in maltreated subjects (Hart and Rubia, 2012). Hypersensitivity to social rejection by strangers might help explain why maltreated (and especially neglected) individuals may exhibit specific difficulties with social relationships, including the parent-child relationships (DeGregorio, 2013).

Exclusion by family

Whole brain analyses showed differential reactivity to social exclusion by strangers versus family. In contrast to our expectations, higher levels of experienced abuse or neglect were not associated with altered BOLD responses in the insula, dACC or dmPFC during exclusion by family for both offspring and parents. It has been reported that mentalizing about strangers activates more dorsal parts of the MPFC, whereas more ventral regions of the MPFC may be activated during mentalization related to close significant others (for example family members) with whom individuals experience self-other overlap (Mitchell *et al.*, 2005; Krienen *et al.*, 2010). We might have missed important brain areas with our selected ROIs, and future research might also include other regions, for instance ventral parts of the PFC.

Generally, rejection by a member of an established in-group is associated with enhanced pain of rejection (Bernstein *et al.*, 2010). Little is known about the neural correlates of family-related entitativity (Rüsch *et al.*, 2014), but lower levels of perceived family-related entitativity in maltreated individuals might explain why they do not show altered neural activity after social exclusion by a family member compared to non-mal-treated individuals. Maltreated individuals may have become relatively insensitive for exclusion by their own family, while showing increased sensitivity for rejection in other situations (e.g., rejection by strangers). Another explanation might be that the presentation of the first name of a family member during the Cyberball game was not strong enough to elicit

a clear (attachment) representation. For future research, it is therefore recommended to also use (neutral) pictures of family members to examine this in more detail.

Perpetrated abuse and neglect

Perpetrated abuse and neglect were not associated with activation in the insula, dACC or dmPFC during exclusion by strangers or family, even though it is suggested that these areas might play a role in parenting behavior (Feldman, 2015). Exploratory analyses (see Supplementary data) did suggest that abusive parents show lower reactivity in the precentral and postcentral gyrus during exclusion by strangers. While the precentral gyrus is mainly thought to control motor function, the postcentral gyrus is mostly known for processing sensory information. However, postcentral gyrus reactivity has also been identified in imaging studies of emotion and has been associated with the recognition of both positive and negative emotions and perspective taking (George *et al.*, 1996; Canli *et al.*, 2002; Hooker *et al.*, 2012; Meyer *et al.*, 2015). The precentral gyrus has also been associated with emotional memory, empathic concern and processing rewarding and aversive stimuli (Canli *et al.*, 2002; Montoya *et al.*, 2012; Meyer *et al.*, 2015). Moreover, the precentral gyrus is thought to be involved in the social monitoring system (SMS), an outer monitoring system enhancing perceptive and cognitive responses to social cues and information including social exclusion (Kawamoto *et al.*, 2015). Altered functioning of the SMS might induce antisocial behavior, including rejection and maltreating behavior. Although specific roles of the pre- and postcentral gyrus in affective processes remain to be examined, reduced activation in these areas might implicate that abusive parents are less sensitive to negative emotional and social stimuli.

Intergenerational transmission of maltreatment

While in our sample intergenerational transmission of abuse was observed, neglect did not appear to be transmitted from one generation to the next. This is likely due to the smaller sample size of this fMRI subsample, since transmission of neglect was found in the complete sample of the 3G study.

Altered neural reactivity to social exclusion by strangers in the insula, ACC and dmPFC was associated with experienced maltreatment, whereas abusive parents showed decreased reactivity in the precentral and postcentral gyrus during exclusion by strangers. Hence, we found different neural correlates of experienced and perpetrated maltreatment and therefore no neural mechanisms playing a role in the transmission of maltreatment were found.

Strengths and limitations

This is the first multigenerational family study in which differential neural effects of (experienced and perpetrated) abuse and neglect are examined, and the role of neural

reactivity to social exclusion by strangers versus family is investigated. Research about the neural correlates of child maltreatment and maltreating parenting behavior in particular is scarce, and our family study design enabled the investigation of intergenerational transmission of maltreatment directly. Another strength is that parent (both fathers and mothers) and child reports of maltreatment were combined to minimize the influence of individual reporter bias. Moreover, our study allowed to differentiate between a general sensitivity for exclusion versus rejection sensitivity in the family context.

A limitation of the current study is the use of retrospective reports to measure maltreatment, which can be subject to recall bias. However, we combined parent and child reports in the maltreatment scores. Moreover, in our paradigm names of family members were used. For future research, pictures of own offspring and parents might be used, although this would decrease standardization of the task. Furthermore, our sample to examine the effects of perpetrated maltreatment was smaller than our sample to assess the effects of experienced maltreatment since only part of the sample were parents.

Conclusion

In sum, we found that exclusion by strangers was especially associated with increased activity in the left insula, while exclusion by a family member was mainly associated with higher activation in the ACC. Furthermore, altered neural reactivity to social exclusion by strangers in the insula, ACC and dmPFC was associated with experienced maltreatment but not with parents' own maltreating behavior, indicating different neural correlates of experienced and perpetrated maltreatment. More specifically, hypersensitivity to social rejection in maltreated individuals was mainly driven by experienced neglect. Furthermore, exploratory analyses showed that abusive parents exhibited lower activation in the pre- and post-central gyrus during exclusion by strangers, possibly reflecting lower levels of perspective taking and empathic abilities. Our study underscores the importance to distinguish between effects of abuse and neglect and suggests that the impact of experiencing rejection and maltreatment by your own parents goes beyond the family context.

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CONFLICT OF INTEREST.

None declared.

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SUPPLEMENT

METHOD

Participants

This sample included 1 parent-child pair with two parents and two offspring (*n* = 4), 12 pairs with two parents and one offspring (*n* = 36), 7 pairs with one parent and two offspring (*n* = 21), 13 pairs with one parent and one offspring (*n* = 26) and 1 pair with two offspring and three parents (two biological parents and a stepfather; *n* = 5). Additionally, 38 parents participated without their offspring and 14 offspring participated without their parents participating. The vast majority of all participants (96.5%) were Caucasian, three participants were of Latin-American descent and two of mixed descent. Elementary school or a short track of secondary school was completed by 30.6% of all participants, 37.5% held an advanced secondary school or vocational school diploma, 17.4% held a college or university degree and 7.6% a postgraduate diploma. 6.9% of all participants were still in elementary school.

Unfamiliar condition: *n* = 72, mean age = 36.2 years, SD = 16.17, age range: 8.8-67.6 years. Parents in the familiar condition: *n* = 41, mean age = 49.3 years; SD = 10.44, age range: 33.9-69.7 years. Children in the familiar condition: *n* = 31, mean age = 22.0 years; SD = 8.63, age range: 9.3-40.1 years.

Childhood maltreatment

For 95 out of 144 participants two informants (participants and their parents) reported on maltreatment history and for 47 participants we only had self-report information on experienced maltreatment, resulting in a total of 237 informants on experienced childhood maltreatment. For 2 participants, information on experienced childhood maltreatment was missing, hence they were only included in the analyses regarding maltreating behavior. Of all 144 participants, 90 had at least one child. For 74 of these 90 participants two informants (participants and their offspring) reported on maltreating behavior, while for the remaining 16 only one informant reported on perpetrated maltreatment (87.5% self-report, 12.5% child report). For one participant, it was not clear whether offspring had reported about their biological parents or their stepparents, hence in these cases child-report information was not included. This resulted in a total of 163 informants on perpetrated maltreatment.

Internal consistencies of the scales were as follows: α_{mother} = .94, α_{father} = .94 for physical abuse, α_{mother} = .82 and α_{father} = .76 for emotional abuse, α_{mother} = .77 and α_{father} = .67 for physical neglect, and α_{mother} = .92, α_{father} = .92 for emotional neglect.

Cyberball task

Prior to the task, participants received the following instruction: "During the game it is really important that you try to imagine yourself actually playing the ball-tossing game as vividly as possible. Try to imagine that you are in a park throwing a ball with two other people." Prior to the start of the game in the scanner, a false Google™ page with a 'Cyberball' listing that was linked to a 'loading screen' was presented to enhance credibility of the game. Each participant got to select their own glove before the start of the game.

fMRI data analysis

The inclusion and exclusion block of the familiar round were both divided in four conditions: 'receiving the ball by a family member', 'not receiving the ball by a family member', 'receiving the ball by a stranger', 'not receiving the ball by a stranger'. The inclusion and exclusion block of the unfamiliar round were divided into the following conditions: 'receiving the ball by a stranger', 'not receiving the ball by a stranger'.

With a more exploratory aim, we included anatomical ROIs of two other regions based on activation at the whole brain level, namely the pre- and postcentral gyrus, using the TD label atlas (Maldjia et al., 2003; see Figure S1). Both areas are also associated with social exclusion (Bolling et al., 2011), perspective-taking and empathy (Meyer et al., 2015).

SPSS data analysis

Composite household SES scores were calculated by averaging standardized household income and standardized completed educational level of both parents living in the same household. Children living with their parents shared the household SES score of their parents.

RESULTS

Leaving out all left-handed participants in our sample (n = 18) did not change the main effects of abuse and neglect.

Exploratory multilevel analyses

Exclusion by strangers

With a more exploratory aim, multilevel regression analyses were repeated with BOLD responses in the pre- and postcentral gyrus as outcome measure and with (experienced and perpetrated) abuse and neglect as predictors (see Supplement Tables S1A and S2A). Adding experiences of abuse and neglect as predictors significantly improved the models for activation in the precentral (χ^2 (2) = 8.42, p = .015) and postcentral gyrus (χ^2 (2) = 9.96,

p = .007) regarding exclusion by strangers. Results showed no unique contribution of experienced abuse or neglect regarding exclusion by strangers.

Adding perpetrated abuse and neglect as predictors significantly improved the model for activation in the postcentral gyrus (χ^2 (2) = 11.07, p = .004), with a negative main effect for perpetrated abuse (p = .001). Additionally, a trend was found for the precentral gyrus model (χ^2 (2) = 5.99, p = .050), with a negative main effect for perpetrated abuse (p = .016).

Exclusion by family

Similar exploratory analyses were run for the familiar contrast (see Supplement Tables S1B and S2B). Adding experienced or perpetrated abuse and neglect as predictors did not improve the models for activation in the pre- and postcentral gyrus regarding exclusion by family. Furthermore, no main effects were found for experienced or perpetrated abuse and neglect regarding activation in the pre- or postcentral gyrus during exclusion by one's own offspring.

Table S1A. Multilevel model of brain reactivity in the precentral gyrus in response to social exclusion as related to experienced and perpetrated abuse and neglect: unfamiliar Cyberball.

Precentral gyrus: Unfamiliar round								
	Experienced maltreatment					Maltreating behavior		
	Parents and offspring (n = 72)					*Parents (n = 45)*		
	b	SE	*p*			*b*	SE	*p*
abused	-3.03	2.09	.152		abusive	-6.80*	2.70	.016
neglected	1.39	2.25	.539		neglectful	3.10	3.09	.321
	χ^2 (2) = 8.42*		.015			χ^2 (2) = 5.99		.050

* $p < .05$; ** $p < .01$

Significant covariates are included in the model (see Supplement)

Table S1B. Multilevel model of brain reactivity in the precentral gyrus in response to social exclusion as related to experienced and perpetrated abuse and neglect: familiar Cyberball.

Precentral gyrus: Familiar round										
	Experienced maltreatment							Maltreating behavior		
	Parents (n = 41)			*Offspring (n = 31)*				*Parents (n = 41)*		
	b	SE	*p*	*b*	SE	*p*		*b*	SE	*p*
abused	0.59	1.25	.641	0.78	2.05	.706	abusive	-0.70	1.75	.691
neglected	-0.14	1.07	.894	-1.04	2.03	.613	neglectful	-0.01	1.50	.997
	χ^2 (2) = 0.22		.896	χ^2 (2) = 0.31		.859		χ^2 (2) = 0.21		.901

* $p < .05$; ** $p < .01$

Significant covariates are included in the model (see Supplement)

Table S2A. Multilevel model of brain reactivity in the postcentral gyrus in response to social exclusion as related to experienced and perpetrated abuse and neglect: unfamiliar Cyberball.

Postcentral gyrus: Unfamiliar round								
	Experienced maltreatment				Maltreating behavior			
	Parents and offspring (n = 72)				*Parents (n = 45)*			
	b	SE	*p*		*b*	SE	*p*	
abused	-4.36	2.79	.123	abusive	-11.70**	3.42	.001	
neglected	1.68	3.00	.578	neglectful	7.49	3.91	.062	
	χ^2 (2)= 9.96**		.007		χ^2 (2) = 11.07**		.004	

* $p < .05$; ** $p < .01$

Significant covariates are included in the model (see Supplement)

Table S2B. Multilevel model of brain reactivity in the postcentral gyrus in response to social exclusion as related to experienced and perpetrated abuse and neglect: familiar Cyberball.

Postcentral gyrus: Familiar round										
	Experienced maltreatment							Maltreating behavior		
	Parents (n = 41)			*Offspring (n = 31)*				*Parents (n = 41)*		
	b	SE	*p*	*b*	SE	*p*		*b*	SE	*p*
abused	0.49	1.56	.758	1.37	2.31	.558	abusive	-2.51	2.05	.228
neglected	0.49	1.35	.721	-1.35	2.37	.573	neglectful	-0.13	1.67	.940
	χ^2 (2) = 0.34		.846	χ^2 (2) = 0.48		.785		χ^2 (2) = 2.04		.360

$p < .05$; ** $p < .01$

Significant covariates are included in the model (see Supplement)

Table S3. Multilevel model of brain reactivity in the left insula in response to social exclusion as related to experienced childhood abuse and neglect.

Left insula									
	Unfamiliar round			Familiar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*	*b*	SE	*p*
Covariates	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* = 31)		
age	0.00	.01	.639	-0.02	.01	.187	0.01	.02	.584
gender	0.23	.30	.452	0.13	.24	.582	0.22	.42	.609
handedness	0.46	.40	.254	0.62	.62	.320	0.48	.71	.504
SES	-0.15	.22	.502	0.37*	.18	.043	0.53	.32	.110
PP	-0.60	.68	.386	0.60	.67	.375	1.44	1.08	.192
Model 1	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* =3 1)		
abused	0.28	1.68	.869	0.70	1.12	.538	3.42	2.65	.207
neglected	2.31	1.65	.167	-0.34	1.02	.740	-0.56	2.67	.836

* $p < .05$; ** $p < .01$

SES = social economic status; PP = psychopathology

Table S4. Multilevel model of brain reactivity in the right insula in response to social exclusion as related to experienced childhood abuse and neglect.

Right insula									
	Unfamiliar round			Familiar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*	*b*	SE	*p*
Covariates	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* = 31)		
age	-0.01	.01	.578	-0.02	.01	.111	0.01	.03	.658
gender	0.20	.31	.518	0.18	.13	.244	0.15	.44	.727
handedness	0.29	.41	.488	0.34	.63	.594	0.33	.75	.660
SES	-0.12	.23	.606	0.43*	.18	.021	0.28	.41	.498
PP	-0.67	.71	.347	1.71**	.50	.006	3.10*	1.19	.013
Model 1	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* = 31)		
abused	-0.17	1.77	.922	0.58	.74	.454	0.57	.78	.485
neglected	1.13	1.73	.516	-0.16	1.02	.877	0.04	1.07	.974

* $p < .05$; ** $p < .01$

SES = social economic status; PP = psychopathology

Table S5. Multilevel model of brain reactivity in the dACC in response to social exclusion as related to experienced childhood abuse and neglect.

dACC									
	Unfamiliar round			Familiar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*	*b*	SE	*p*
Covariates	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* = 31)		
age	-0.01	.011	.236	-0.03	.02	.124	-0.02	.02	.317
gender	0.256	.37	.497	0.59	.32	.070	-0.09	.39	.827
handedness	-0.56	.50	.265	0.64	.75	.400	-1.68*	.64	.014
SES	0.07	.28	.803	0.19	.22	.395	-0.60	.30	.051
PP	0.17	.85	.842	0.67	.84	.427	0.30	.97	.763
Model 1	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* = 31)		
abused	-2.72	2.12	.206	1.04	1.52	.497	1.36	2.47	.586
neglected	2.61	2.05	.207	-0.28	1.34	.836	-0.80	2.43	.745

* $p < .05$; ** $p < .01$

SES = social economic status; PP = psychopathology

Table S6. Multilevel model of brain reactivity in the dmPFC in response to social exclusion as related to experienced childhood abuse and neglect.

dmPFC									
	Unfamiliar round			Familiar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*	*b*	SE	*p*
Covariates	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* = 31)		
age	0.02	.01	.078	-0.01	.02	.570	-0.02	.02	.419
gender	0.28	.38	.475	-0.26	.34	.453	0.37	.45	.417
handedness	0.36	.50	.481	1.37	.86	.123	0.36	.74	.627
SES	-0.30	.28	.290	0.17	.26	.526	0.32	.34	.347
PP	-1.25	.86	.154	0.79	.97	.424	0.69	1.11	.539
Model 1	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* = 31)		
abused	1.17	2.16	.591	0.82	1.75	.640	-2.19	2.71	.426
neglected	2.50	2.12	.242	-3.26*	1.52	.038	1.36	2.68	.616

* $p < .05$; ** $p < .01$

SES = social economic status; PP = psychopathology

Table S7. Multilevel model of brain reactivity in the left insula in response to social exclusion as related to perpetrated childhood abuse and neglect.

Left insula						
	Unfamiliar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*
Covariates	Parents (*n* = 41)			Parents (*n* = 41)		
age	0.02	.02	.335	-0.02	.01	.183
gender	0.23	.36	.518	0.03	.21	.873
handedness	0.81	.58	.169	0.43	.42	.315
SES	-0.07	.32	.825	0.29	.18	.107
PP	0.11	.87	.897	0.14	.63	.824
Model 1	Parents (*n* = 45)			Parents (*n* = 41)		
abusive	3.01	2.12	.162	0.62	1.75	.724
neglectful	-2.86	2.38	.236	-0.22	1.27	.861

* $p < .05$; ** $p < .01$

SES = social economic status; PP = psychopathology

Table S8. Multilevel model of brain reactivity in the right insula in response to social exclusion as related to perpetrated childhood abuse and neglect.

Right insula						
	Unfamiliar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*
Covariates	Parents (*n* = 41)			Parents (*n* = 41)		
age	0.00	.02	.909	-0.03**	.01	.003
gender	0.18	.40	.655	0.16	.12	.224
handedness	0.64	.64	.322	0.24	.24	.323
SES	-0.06	.34	.860	0.35	.18	.060
PP	-0.29	.96	.765	1.50**	.44	.004
Model 1	Parents (*n* = 45)			Parents (*n* = 41)		
abusive	0.78	2.20	.725	0.71	1.57	.656
neglectful	-5.17*	2.46	.041	-0.41	1.03	.699

* $p < .05$; ** $p < .01$

SES = social economic status; PP = psychopathology

Table S9. Multilevel model of brain reactivity in the dACC in response to social exclusion as related to perpetrated childhood abuse and neglect.

dACC						
	Unfamiliar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*
Covariates	Parents (*n* = 41)			Parents (*n* = 41)		
age	-0.02	.02	.484	-0.03	.02	.062
gender	0.83	.46	.082	0.64*	.31	.044
handedness	-0.59	.74	.429	0.05	.63	.941
SES	-0.13	.40	.745	0.09	.20	.676
PP	1.33	1.11	.240	0.43	.82	.602
Model 1	Parents (*n* = 45)			Parents (*n* = 41)		
abusive	-4.59	2.70	.096	-0.84	2.03	.683
neglectful	1.34	3.03	.660	0.73	2.05	.725

* $p < .05$; ** $p < .01$

SES = social economic status; PP = psychopathology

Table S10. Multilevel model of brain reactivity in the dmPFC in response to social exclusion as related to perpetrated childhood abuse and neglect.

dmPFC						
	Unfamiliar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*
Covariates	Parents (*n* = 41)			Parents (*n* = 41)		
age	0.01	.02	.609	-0.00	.02	.944
gender	0.56	.49	.262	-0.20	.32	.539
handedness	0.71	.78	.367	0.65	.64	.328
SES	-0.27	.42	.519	0.26	.26	.321
PP	-0.35	1.17	.770	1.16	.92	.217
Model 1	Parents (*n* = 45)			Parents (*n* = 41)		
abusive	4.12	2.82	.151	-2.08	2.43	.396
neglectful	-3.03	3.16	.343	1.83	2.13	.396

* $p < .05$; ** $p < .01$

SES = social economic status; PP = psychopathology

Table S11. Multilevel model of brain reactivity in the precentral gyrus in response to social exclusion as related to experienced childhood abuse and neglect.

Precentral gyrus									
	Unfamiliar round			Familiar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*	*b*	SE	*p*
Covariates	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* = 31)		
age	-0.02	.01	.091	-0.02	.01	.174	-0.01	.02	.646
gender	0.40	.35	.263	0.28	.28	.315	0.24	.35	.490
handedness	-1.03*	.48	.035	0.64	.65	.328	-0.18	.57	.755
SES	0.25	.27	.362	0.11	.18	.552	-0.62	.26	.025
PP	0.80	.81	.327	0.61	.72	.404	-0.22	.86	.797
Model 1	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* = 31)		
abused	-3.03	2.09	.152	0.59	1.25	.641	0.78	2.05	.706
neglected	1.39	2.25	.539	-0.14	1.07	.894	-1.04	2.03	.613

* $p < .05$; ** $p < .01$

SES = social economic status; PP = psychopathology

Table S12. Multilevel model of brain reactivity in the postcentral gyrus in response to social exclusion as related to experienced childhood abuse and neglect.

Postcentral gyrus									
	Unfamiliar round			Familiar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*	*b*	SE	*p*
Covariates	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* = 31)		
age	-0.02	.01	.130	-0.01	.02	.684	-0.03	.02	.190
gender	0.63	.48	.195	0.66	.33	.058	0.23	.33	.482
handedness	-1.52*	.63	.019	0.36	.82	.664	-0.16	.52	.752
SES	0.25	.36	.480	0.06	.23	.800	-0.81*	.31	.013
PP	0.38	1.08	.725	0.27	.91	.771	-0.46	.92	.618
Model 1	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* = 31)		
abused	-4.36	2.79	.123	0.49	1.56	.758	1.37	2.31	.558
neglected	1.68	3.00	.578	0.49	1.35	.721	-1.35	2.37	.573

* $p < .05$; ** $p < .01$

SES = social economic status; PP = psychopathology

Table S13. Multilevel model of brain reactivity in the precentral gyrus in response to social exclusion as related to perpetrated childhood abuse and neglect

Precentral gyrus						
	Unfamiliar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*
Covariates	Parents (*n* = 41)			Parents (*n* = 41)		
age	-0.04	.02	.121	-0.02	.01	.127
gender	1.14*	.47	.021	0.31	.26	.241
handedness	-1.03	.77	.189	0.15	.52	.772
SES	0.20	.43	.645	0.05	.17	.785
PP	1.08	1.14	.350	0.41	.70	.562
Model 1	Parents (*n* = 45)			Parents (*n* = 41)		
abusive	-6.80*	2.70	.016	-0.70	1.75	.691
neglectful	3.10	3.09	.321	-0.01	1.50	.997

* $p < .05$; ** $p < .01$

SES = social economic status; PP = psychopathology

Table S14. Multilevel model of brain reactivity in the postcentral gyrus in response to social exclusion as related to perpetrated childhood abuse and neglect

Postcentral gyrus						
	Unfamiliar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*
Covariates	Parents (*n* = 41)			Parents (*n* = 41)		
age	-0.06	.03	.058	-0.01	.02	.618
gender	1.65*	.62	.011	0.71*	.29	.025
handedness	-1.68	1.01	.104	-0.05	.57	.934
SES	0.30	.57	.599	0.017	.22	.941
PP	1.07	1.49	.479	-0.12	.84	.890
Model 1	Parents (*n* = 45)			Parents (*n* = 41)		
abusive	-11.70**	3.42	.001	-2.51	2.05	.228
neglectful	7.49	3.91	.062	-0.13	1.67	.940

* $p < .05$; ** $p < .01$

SES = social economic status; PP = psychopathology

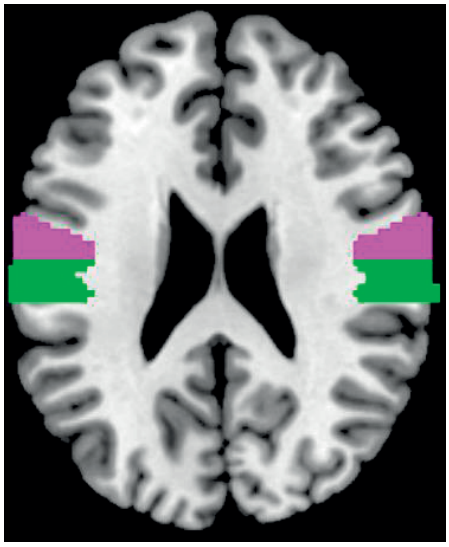
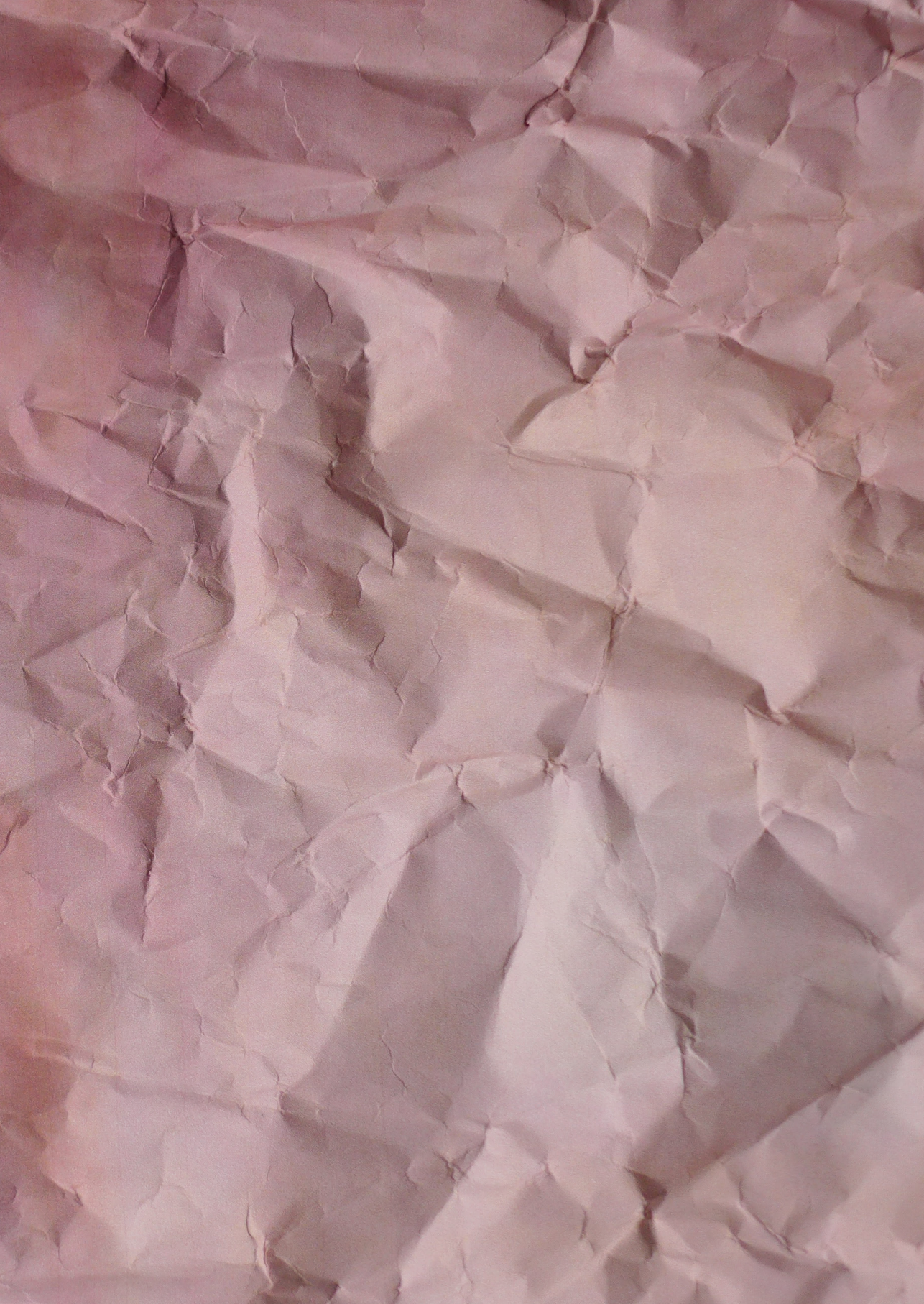


Figure S1. ROI masks of exploratory ROIs.
Purple: anatomical precentral gyrus ROI mask; Green: anatomical postcentral gyrus ROI mask.



Chapter 6

Discussion

The primary objective of the current dissertation was to investigate the impact of different types of traumatic (A1) and stressful (non-A1) life events, including a focus on the impact of child abuse and neglect. The role of structural and functional neural correlates of threat processing in intergenerational transmission of child maltreatment (ITCM) was examined using a family study design. A summary of our findings and conclusions will first be presented, followed by limitations, future directions, clinical implications and a general conclusion.

TRAUMATIC EVENTS VERSUS STRESSFUL LIFE EVENTS

The incidence rate of stressful and potentially traumatic events is high (Kessler et al., 2017; Kilpatrick et al., 2013; Thordardottir et al., 2015) and the impact of stress and trauma on our emotional, psychological and physical wellbeing can be devastating. Experiencing traumatic (A1) events (as defined according to the DSM) can not only lead to posttraumatic stress disorder (PTSD), but has also been repeatedly associated with the aetiology and maintenance of other forms of psychopathology (e.g., Mauritz, Goossens, Draijer, & Van Achterberg, 2013; Shonkoff & Garner, 2012). However, there is more uncertainty about the impact of non-A1, but still severely stressful, life events. There has been an ongoing discussion about the clinical usefulness and validity of the A1 criterion of PTSD, since studies showed that stressful non-A1 life events are associated with similar or even higher levels of PTSD symptoms than formal A1 events (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).

In Chapter 2, a study was described investigating whether formal DSM-IV-TR traumatic (A1; e.g., a life-threatening illness or injury, or physical and sexual assault) and stressful (non-A1) life events (e.g., family problems, bullying or emotional neglect) differ with regard to PTSD symptom profiles, and whether there is a gender difference in this respect. In a large, mostly clinical sample from the NESDA study (n = 1433) we found that PTSD symptoms were equally or even more severe in participants reporting non-A1 events than A1 events as their index event (i.e., their most bothersome event). Remarkably, 86% of all participants from the non-A1 event group (participants who reported a non-A1 event as their index event) indicated to be bothered by intrusions, avoidance of event-related cues and/or heightened arousal related to their index event during the past five years versus 50% of the A1 event group (participants who reported an A1 event as their index event). In the light of these findings it is remarkable that it was decided to narrow the A1 criterion of PTSD in the DSM-5 so 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 (American Psychiatric Association, 2013).

Our findings are in line with previous research (e.g., Anders et al., 2011; Gold et al., 2005; Mol et al., 2005) and emphasize the need to pay closer attention to PTSD symptom profiles rather than the strict definition of the A1 criterion in clinical practice to prevent highly symptomatic individuals being excluded from treatment, following the course of the ICD-11 (WHO, 2018). While the ICD-11 also requires exposure to a traumatic event for a PTSD diagnosis, the nature of those events is considered as a risk factor instead of a requirement leaving room for the role of genetic and environmental risk and resilience factors in differential responses to potentially traumatic events (Hyland et al., 2017).

The role of gender in PTSD symptomatology

Another important aim of the study presented in Chapter 2 was to investigate how gender may affect the link between type of experienced event and PTSD symptomatology. Women develop PTSD about twice as often as men (e.g, Christiansen & Elklit, 2012; Olff, Langeland, Draijer, & Gersons, 2007; Tolin & Foa, 2008) and are overrepresented in chronic PTSD cases (Breslau & Davis, 1992) despite their lower overall likelihood to experience potentially traumatic events (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; Tolin & Foa, 2008). Those findings appear to reflect substantive differences between men and women (Christiansen & Elklit, 2012; Chung & Breslau, 2008; Tolin & Foa, 2008). However, it is unknown whether this increased vulnerability in women also extends to non-A1 events.

Looking at our findings in Chapter 2, it was striking that whereas in the A1 event group women showed significantly higher PTSD symptoms than men (29.9% versus 15.4% met PTSD B, C and D criteria) in line with previous studies (e.g., Tolin & Foa, 2008), in the non-A1 event group there were no gender differences in PTSD symptoms (women: 28.2%; men: 31.3%). Moreover, for women PTSD symptom severity on any of the PTSD symptom clusters was the same in both groups. Men who experienced a non-A1 index event even showed significantly higher PTSD scores than men whose index event was an A1 event. Men reported more intrusions, arousal and especially higher levels of avoidance symptom severity after non-A1 versus A1 events.

To date, little is known about the mechanisms behind gender differences in PTSD development. There is a serious lack of evidence on gender specific appraisal processes of trauma (e.g., Olff et al., 2007). Furthermore, the impact of childhood adversity and trauma in men has received less attention in previous studies, probably because of its seemingly lower prevalence rates and less overt symptom presentation (Sweeney, Air, Zannettino, Shah, & Galletly, 2015). It is important to gain more insight into these gender mechanisms, because they could help us understand why some individuals adjust to trauma and recover from the emotional burden that follows and others experience mental health problems and develop PTSD. This way, learning more about the mechanisms behind gender differences in PTSD development might provide guidance for the development of preventive interventions in clinical practice.

While examining potential underlying mechanisms of gender differences with respect to the impact of event type and PTSD symptoms in our study, we could exclude a few candidate factors, including comorbid psychopathology and number of recently experienced negative life events. We did find that women report higher levels of anxiety and perceived impact of either type of events than men. However, although this might partly explain the higher PTSD scores in women compared to men after experiencing A1 events, this cannot explain the lack of gender differences in PTSD symptoms after non-A1 events and contradicts the finding that men experience more PTSD symptoms after non-A1 versus A1 events.

It seems likely that gender differences regarding PTSD are due to factors that are not examined in most studies such as certain aspects of the experienced events itself, pre-existing cognitive and emotional reactions to potentially traumatic events and a tendency toward different expressions of distress in men and women (Craske, 2003; Tolin & Foa, 2008). While classifying potentially traumatic events into a few broad categories is done in most PTSD studies, it carries the risk of overlooking potentially important gender-specific differences with regard to experienced events (Tolin & Foa, 2008). Although the events experienced by men and women may fall into roughly the same event category, men and women tend to experience the same type of traumatic events in a different way. For instance, men who experienced sexual abuse during childhood are more likely to have experienced physical force or threats during the abuse, while women are more likely to experience sexual abuse multiple times and are more often abused by a close family member. This illustrates that it might be relevant for future studies to zoom in into different types of potentially traumatic events to help clarify gender differences in PTSD.

Moreover, cognitive differences between men and women might also play a role. Negative posttraumatic cognitions regarding oneself, the world, or self-blame can generate an ongoing feeling of threat which is critical to develop PTSD and associated with PTSD symptom severity (Blain, Galovski, Elwood, & Meriac, 2013; Ehlers & Clark, 2000). It was found that women who experienced a potentially traumatic event report higher levels of self-blame following the experienced event, a greater belief of being incompetent or damaged, and a greater belief that the world is a dangerous place compared to men who experienced a potentially traumatic event (Cromer & Smyth, 2010; Daie-Gabai, Aderka, Allon-Schindel, Foa, & Gilboa-Schechtman, 2011; Moser, Hajcak, Simons, & Foa, 2007; Tolin & Foa, 2002). While Moser and colleagues (2007) state that gender differences in PTSD severity remain after controlling for such posttraumatic cognitions, more research is needed to examine whether those cognitions might play a role in PTSD gender differences.

Another cognitive factor that might be important here is the use of different stress-regulating coping strategies. Interestingly, men reported remarkably high levels of avoidance after experiencing non-A1 compared to A1 events (Chapter 2). Previous research shows that avoidance coping, as an emotion regulation strategy, is prospectively associated with PTSD development and maintenance following traumatic exposure (e.g.,

Chawla & Ostafin, 2007; Hayes, Wilson, Gifford, Follette, & Strosahl, 1996) for instance by preventing exposure to corrective information and interfering with emotional processing (Schick, Weiss, Contractor, Suazo, & Spillane, 2020). It is possible that men show higher levels of avoidance after non-A1 life events because it is less socially accepted for men to be affected by events that are not officially classified as traumatic. Preexisting socially influenced gender differences regarding responses to and coping with stress and trauma might be triggered after experiencing a non-A1 event, resulting in different posttraumatic symptom patterns in men and women. It is recommended for future research to examine the role of those factors into more detail.

Furthermore, the timing of stress and trauma might be associated with the impact later in life (Murgatroyd et al., 2009; Oberlander et al., 2008). Unfortunately, we do not have information about the timing of the traumatic and stressful events that were reported in our study. Since research shows that types of interpersonal trauma that are frequently reported by women tend to occur at a younger age and increase risk for revictimization (Lilly & Valdez, 2012), we recommend to examine timing of traumatic and stressful life events in future research as a possible explanation of gender differences in PTSD symptomatology.

Gender differences regarding PTSD might also be related to hormonal differences in men and women (Goldstein, Holsen, Handa, & Tobet, 2014). Higher concentrations of testosterone in men versus higher levels of estrogens in women might moderate how men and women respond to stressful and potentially traumatic events (e.g., Fink, Sumner, Rosie, Grace, & Quinn, 1996; Gillies, & McArthur, 2010; Steiner, Dunn, & Born, 2003). Finally, gender differences in PTSD might also reflect a more general vulnerability for affective disorders in women, since depression and anxiety disorders are more common among women compared to men (Kessler et al., 2005).

All and all, the factors involved in gender differences in PTSD are complex (Møller, Augsburger, Elklit, Søgaard, & Simonsen, 2020) and it seems plausible that an interplay of factors linked to differential (subjective) experience and evaluation of the stressful and (potentially) traumatic experiences rather than more objective features of trauma such as the type of trauma are at play. Future research should gain more insight into the mechanisms behind these important gender differences and should focus on pre-, peri- and posttraumatic risk factors (Christiansen & Hansen, 2015; Tolin & Foa, 2008).

CHILD MALTREATMENT

In the second part of this dissertation (Chapter 3, 4 and 5) we focused on the impact of one of the most common types of childhood trauma, namely childhood abuse and neglect (e.g., Martins, De Carvalho Tofoli, Von Werne Baes, & Juruena, 2011). Individuals who experienced child maltreatment are at high risk to develop PTSD and other (comorbid) psy-

chopathology (e.g., De Bellis & Thomas, 2003). Moreover, experienced child maltreatment is associated with long-lasting negative psychological, emotional, neural and behavioral alterations, which can influence future parenting behavior (e.g., Van Wert, Anreiter, Fallon, & Sokolowski, 2019). One of the striking consequences of experienced childhood maltreatment is the increased risk of maltreating own offspring (e.g., Dubowitz et al., 2001; Madigan et al., 2019; Savage, Tarabulsy, Pearson, Collin-Vézina, & Gagné, 2019). The rates of this transmission vary substantially across different studies (Dixon, Hamilton-Giachritsis, & Browne, 2005; Egeland, Jacobvitz, & Sroufe, 1988; Pears & Capaldi, 2001), highlighting the lack of clarity regarding this issue and the methodological difficulties inherent to studying parenting across generations (Van Wert et al., 2019). However, whereas the ITCM hypothesis is confirmed in a recent umbrella synthesis of meta-analyses (Van IJzendoorn, Bakermans-Kranenburg, Coughlan, & Reijman, 2020), to date little is known about the mechanisms behind this cycle of maltreatment (Alink, Cyr, & Madigan, 2019). In the current dissertation the neural correlates of ITCM were examined using a multi-informant, multigenerational family study called the 3-Generation (3G) Parenting Study (total *n* = 395). By investigating associations between brain structure and function with experienced and perpetrated child abuse and neglect we aimed to gain more insight in the possible mediating role of neural correlates of threat processing in ITCM.

STRUCTURAL AND FUNCTIONAL NEURAL CORRELATES OF EXPERIENCED CHILD MALTREATMENT

Hippocampal volume

In Chapter 3 we examined the role of brain structure in ITCM. We chose to focus on the hippocampus, because of its plasticity and sensitivity to stress (McEwen, 2010) and its important role in the limbic system. Moreover, experienced childhood maltreatment has repeatedly been associated with reduced hippocampal volume (e.g., McCrory, De Brito, & Viding, 2011; Riem, Alink, Out, Van IJzendoorn, & Bakermans-Kranenburg, 2015; Teicher et al., 2018; Whittle et al., 2016) and enhanced stress reactivity in the hippocampus across the lifespan (Kim et al., 2010a). The hippocampus also seems to be involved in normative parenting behavior (Swain, Lorberbaum, Kose, & Strathearn, 2007). However, it was unknown whether hippocampal volume alterations are associated with maltreating parenting behavior as well and hence, whether it might play a role in ITCM. This was examined in the 3G Parenting Study including 180 participants from two generations (parents and their offspring) of 53 families. We found associations between experienced child abuse and reduced hippocampal volume, but only in men. That is, men who experienced more abuse during their childhood showed smaller bilateral hippocampal volume than men

who experienced less childhood abuse, with more pronounced effects in the right hippocampus.

In previous studies reductions in hippocampal volume are more often reported in maltreated adults than in maltreated children and adolescents (Anderson & Teicher, 2004; Teicher & Samson, 2016; Whittle et al., 2016), pointing to the presence of a so-called "sleeper effect" of trauma (Briere, 1992). However, some researchers found that alterations in hippocampal development can already become evident a few years after maltreatment experiences in children (De Bellis, Hall, Boring, Frustaci, & Moritz, 2001; Luby et al., 2013; Whittle et al., 2013) and persist into adulthood, even in healthy individuals without psychopathology (Dannlowski et al., 2012). These mixed findings call for more research regarding the timing of the effects of maltreatment experiences on hippocampal volume reductions. In the 3G Parenting study a sample with a wide age range (8-70 years) was included to help clarify the inconsistent findings regarding hippocampal volume in maltreated children and adolescents compared to adults (De Bellis et al., 1999; Edmiston et al., 2011; Tupler & De Bellis, 2006). This large age range allowed for a closer look at the role of age, although our design is not suitable to examine the exact timing of the effects.

In general, irrespective of maltreatment, lower bilateral hippocampal volumes were found in older participants in our sample. While previous estimates of age-related hippocampal volume loss vary across different studies, almost all studies report negative correlations between age and hippocampal volume (for a review see Van Petten, 2004; Erickson et al., 2010; Raz et al., 2005). Importantly though, no interaction effects between experienced maltreatment and age were found in our study. A within-subject longitudinal setup might further examine any age effects of the impact of experienced maltreatment, but our results suggest that the effect of experienced abuse on hippocampal volume in men may be independent of age, arguing against the presence of a sleeper effect.

Furthermore, the finding that hippocampal volume in men was only associated with experienced abuse and not with experienced neglect is consistent with previous research showing reduced hippocampal volume 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), highlighting the importance to differentiate between the impact of different types of child maltreatment.

Neural reactivity to emotional faces

Decoding affective signals, recognizing emotions and detecting signs of threat is very important for the development of children (Masten et al. 2008; Shenk, Putnam, & Noll, 2013). Research shows that early adverse experiences can interfere with this learning process leading to emotion regulation difficulties, impaired empathy and social skills (e.g., Assed et al., 2020; Dackis, Rogosch, & Cicchetti, 2015; Kim & Cicchetti, 2010). Although sensitivity to recognize negative emotional expressions and signs of threat serves as a potentially

adaptive skill for children growing up in a hostile environment (Pollak, Cicchetti, Hornung, & Reed, 2000), this hypersensitivity has been linked to the development of psychopathology and problems with interpersonal relationships throughout their development (Cicchetti, Toth, & Maughan, 2000).

Experienced child maltreatment is associated with difficulties with emotional reactivity and processing (e.g., Briere, 2002; Pozzi et al., 2020) characterized by problems with expressing and recognizing emotions and a hypervigilance to (negative) emotional faces (e.g., Assed et al., 2020; Pollak & Tolley-Schell, 2003). Moreover, those emotion regulation deficits seem to be reflected in chronic functional and structural alterations in two brain regions involved in socio-emotional processing, namely frontal and limbic areas (Hart & Rubia, 2012; Hein & Monk, 2017). Differential neural face processing in individuals who experienced child maltreatment has previously 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 inferior frontal gyrus (IFG; Hart et al., 2018).

In Chapter 4 we set out to investigate whether we could replicate those findings in our large multigenerational 3G Parenting Study sample including 171 participants of 51 families of two generations with a large age range (8-69 years). The association between experienced childhood abuse and neglect and neural reactivity in the amygdala, hippocampus, IFG and insula in response to emotional (angry, fearful and happy) and neutral faces was examined. Our findings indicate that neural reactivity to emotional faces in the amygdala and IFG is associated with experienced childhood maltreatment and point to differential effects for experienced abuse and neglect, depending on current age. Results showed enhanced bilateral amygdala activation in response to fearful faces in older neglected individuals, whereas reduced amygdala activation was found in younger neglected individuals. In line with results of previous studies (e.g., Maheu et al., 2010; Van Harmelen et al., 2013), this indicates a hypervigilance to negatively valenced faces in neglected adults. Decreased amygdala activation in younger neglected individuals is in line with findings in children from risky families showing low amygdala reactivity to emotional faces (Taylor, Eisenberger, Saxbe, Lehman, & Lieberman, 2006) and with longitudinal research showing that amygdala reactivity to negatively valenced faces increases across adolescence in offspring who experienced high levels of stressful life events (Swartz, Williamson, & Hariri, 2015).

The fact that we did not find associations between amygdalar and hippocampal activation with experienced abuse highlights the need to differentiate between the neural impact of child abuse and neglect. Most previous studies did not disentangle different forms of child maltreatment (e.g., Hart and Rubia, 2012) or only focused on child abuse (e.g., Stoltenborgh et al., 2013). Differential findings for abuse and neglect were also found regarding IFG reactivity. While experienced abuse was associated with lower IFG activation while viewing fearful, happy and neutral faces in younger individuals, experience of ne-

glect was associated with higher IFG activation in this age group while viewing these faces. These effects disappeared with increasing age. The results of our study are also in line with researchers stating that neglected children have poor valence discriminatory abilities for emotional faces (e.g., Pollak et al., 2000; Van Harmelen et al., 2013; Vorria et al., 2006). Our results might indicate that children who experienced neglect have to work harder to process emotional faces since neglectful parents offer them fewer opportunities in learning to interpret emotional signals. On the other hand, children with abusing parents are more often exposed to behavior that might induce anxiety and hypervigilance which might explain our opposite findings regarding experienced abuse and neglect (Bousha & Twentyman, 1984; Crittenden, 1981; Pollak et al., 2000). Research shows that differential experiences with facial emotional expressions indeed induce different emotional processing strategies (Young & Widom, 2014).

The finding that all effects of experienced abuse and neglect on neural reactivity to emotional and neutral faces were moderated by age in our study indicates age-dependent sensitivity of the amygdala and IFG during face perception in maltreated individuals. A possible explanation might be that offspring up to 18 years old are generally still living at home with their (possibly maltreating) parents, which is usually not the case for older individuals. Altered brain reactivity to emotional faces in these younger individuals might reflect temporary disengagement or even emotional avoidance of emotional faces, to cope with current threat, which may disappear with time when they leave the threatening situation. This may be adaptive in an adverse environment. Depending on age, the experience of maltreatment might also be perceived differently, because of cohort effects, alteration of memories with time, or other buffering factors in older individuals who are not currently experiencing maltreatment (e.g., having been in therapy).

Although childhood maltreatment at any age can result in long-lasting consequences, there might be effects of timing of the experienced maltreatment on developmental windows (known as sensitive periods) for certain brain structures such as the IFG, which might have contributed to our findings. There are indeed several studies reporting sensitive exposure periods of brain regions and interconnecting neural pathways involved in emotion perception and regulation, including the amygdala and prefrontal cortex (e.g., Teicher & Samson, 2016). A recent systematic review confirms that the age of onset of maltreatment experiences can lead up to distinctive pathways towards differential psychological, behavioral, neurobiological and/or physiological outcomes (Assed et al., 2020), including the risk to transmit maltreatment to the next generation. For example, it is suggested that maltreatment experienced during early adolescence and continuous maltreatment from childhood into adolescence are associated with higher chances to become a maltreating parent, whereas childhood-limited maltreatment is not (Thornberry & Henry, 2013).

The fact that we did not measure the exact timing of reported maltreatment experiences and behavior limits the possibility to draw any conclusions about the effects of

maltreatment during specific developmental windows. Although it will be challenging to delineate specific sensitive periods in development when maltreatment has more robust consequences on neurobiology, future research investigating the timing of maltreatment and associated outcomes is warranted. So far, a clear developmental perspective across the life span on the neural basis of threat processing in maltreated individuals is missing, and our findings emphasize that future research using samples with a large age range might reveal important insights into this issue.

Neural reactivity to social rejection

In Chapter 5 we examined the potential role of the neural correlates of threat processing in ITCM while focusing on another relevant process in the context of stressful family environments, namely social rejection, using our large multigenerational sample of the 3G Parenting study (n = 144). Parental rejection of needs for attention and nurturance is an important aspect of child maltreatment (Bolger & Patterson, 2001; Glaser, 2002), which can occur through parental aggression and hostility or via parental neglect and indifference (Loue, 2005). The experience of being rejected by your own parents can generate a more general hypersensitivity for social rejection in all sorts of situations, including next-generation parent-child interactions. Previous researchers found that maltreated individuals show altered neural responses to social rejection (e.g., Van Harmelen et al., 2014). In Chapter 5 we firstly examined whether we could replicate those findings and studied neural responses to social exclusion by strangers versus family members in the insula, dACC and dmPFC in maltreated offspring and their parents using the Cyberball task. All participants played one round of this virtual ball-tossing game with strangers and another round with a family member (and a stranger). For offspring, this family member was their own mother, and parents played with their oldest child. During this game, each player was represented by their first name above a picture of a baseball glove.

Maltreated individuals showed higher activity in the left and right insula and the dmPFC and lower reactivity in the dACC during social exclusion by strangers. Higher activity in the left insula and dmPFC during social exclusion by strangers was especially associated with experienced neglect. Increased dmPFC reactivity to social exclusion in neglected individuals indicates that experienced neglect is associated with increased levels of self- and other-referential processing after social exclusion (e.g., Gusnard, Akbudak, Shulman, & Raichle, 2001; Kelley et al., 2002; Mitchell, Macrae, & Banaji, 2005). Lower dACC reactivity might indicate avoidant or dissociative responses in maltreated individuals (Herringa et al., 2013; Krause-Utz et al., 2012; Puetz et al., 2016). Altered insula activation seems to be associated with deficits in emotion processing in maltreated subjects (Hart and Rubia, 2012), because the insula is linked to various functions including self-awareness and (negative) emotion processing (Kim, Strathearn, & Swain, 2016; Phan, Wager, Taylor, & Liberzon, 2002). The finding of hypersensitivity to social rejection by strangers might help

explain why maltreated (and especially neglected) individuals are more likely to exhibit difficulties with social relationships, including the parent-child relationship (DeGregorio, 2013).

Against our expectations, higher levels of experienced abuse or neglect were not associated with altered neural reactivity during exclusion by family for both offspring and parents. Generally, rejection by a member of an established in-group such as a family member is associated with increased levels of pain of rejection (Bernstein, Sacco, Young, Hugenberg, & Cook, 2010). However, little is known about the neural correlates of family-related entitativity (Rüsch et al., 2014). It could be the case that maltreated individuals perceive lower levels of family-related entitativity. They might have become relatively insensitive to exclusion by their own family members, whereas their rejection sensitivity in other situations (e.g., rejection by strangers) increased. Moreover, we cannot rule out the possibility that differences may be found elsewhere in the brain. For instance, more ventral regions of the mPFC have been associated with mentalization related to close significant others with whom individuals experience self-other overlap (Krienen, Tu, & Buckner, 2010; Mitchell et al., 2005). Hence, future research should therefore also include other brain regions, such as those ventral parts of the mPFC. A third explanation might be that presenting the first name of a family member during the Cyberball game did not provoke a clear (attachment) representation. For future research, it is therefore recommended to use (neutral) pictures of family members to examine this in more detail.

Gender and child maltreatment

As described above in the context of PTSD symptomatology, gender differences are likely to contribute to the outcomes of trauma, and childhood trauma in particular (Sweeney et al., 2015). On a behavioral level, childhood trauma has for example been associated with higher levels of self-reported poor health in men and with higher levels of depression in women (Sweeney, Air, Zannettino, Shah, & Galletly, 2015). On a neural level, gender differences in structural (e.g., Calem, Bromis, McGuire, Morgan, & Kempton, 2017; De Bellis, 2005; Paquola, Bennett, & Lagopoulos, 2016; Samplin, Ikuta, Malhotra, Szeszko, & Derosse, 2013) and functional (e.g., Von Der Heide, Skipper, Klobusicky, & Olson, 2013) neural alterations following experienced child maltreatment have been reported. For instance, maltreated women tend to show greater neural deficits in circuits underlying emotion regulation (Edmiston et al., 2011; Herringa et al, 2013). Also, women seem to be more vulnerable to stress-induced changes in the HPA axis (Weiss, Longhurst, & Mazure, 1999) than maltreated men (Lippard & Nemeroff, 2020). However, to date, few studies examined gender differences following experienced child maltreatment.

The fact that we only found reduced hippocampal volume in abused men in Chapter 3 is consistent with previous studies showing that the male hippocampus is more sensitive to stress than the female hippocampus (e.g., Everaerd et al., 2012; McEwen, 2002;

Samplin et al., 2013; Teicher & Samson, 2016; Whittle et al., 2016). This might be due to the potential protective effect of estrogen in women (McEwen, 2010) and dimorphic differences in developmental trajectory (Teicher et al., 2018). There were no direct indications for gender effects regarding neural reactivity to emotional faces or social rejection since gender was (almost) never significant as a covariate in those analyses (Chapter 4 and 5). Given the already large number of analyses we chose not to investigate gender effects any further in those studies. More research on gender differences regarding the impact of child abuse and neglect, including underlying neurobiological mechanisms, is crucial because it might contribute to unravelling the mechanisms behind ITCM.

STRUCTURAL AND FUNCTIONAL NEURAL CORRELATES OF MALTREATING PARENTING BEHAVIOR

To the best of our knowledge the 3G Parenting Study was the first to examine the association between abusing and neglecting parenting behavior and brain structure and function using a multi-generational family study. While we know that structural and functional neural alterations following experienced child maltreatment span across brain regions that are also involved in caregiving behavior (including the amygdala, hippocampus, insula and IFG; Barrett et al., 2012; 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 (León et al., 2019; Pozzi et al., 2020; Van IJzendoorn et al., 2020).

Our findings in Chapter 3 provide indications that parental abusive or neglectful behavior is not associated with hippocampal volume. It could be that the role of hippocampal volume in maltreating parents with a history of maltreatment is masked by compensatory changes in other brain regions (e.g., Galinowski et al., 2015; Van der Werff, Van den Berg, Pannekoek, Elzinga, & Van der Wee, 2013). This underlines the importance for future studies to also include other brain areas that might play a role in maltreating parenting behavior, for example the corpus callosum, the anterior cingulate and the dorsolateral prefrontal cortex. Results of Chapter 4 and 5 indicate that parental abusive or neglectful behavior is not associated with amygdala, hippocampus, IFG or insula reactivity to emotional or neutral faces, nor with reactivity in the insula, dACC or dmPFC during exclusion by strangers or family members. However, our exploratory analyses in Chapter 5 suggest that abusive parents show lower reactivity in the precentral and postcentral gyrus during exclusion by strangers. Although specific roles of the pre- and postcentral gyrus in affective processes remain to be examined, decreased activation in these areas suggests that abusive parents are less sensitive to negative emotional and social stimuli. Since the precentral gyrus has also been suggested as being an important structure of the maternal

brain in other research (Kim et al., 2010b), future research should further investigate the role of those areas in maltreating parenting behavior.

While structural and functional neural correlates of experienced abuse and neglect were found in the 3G Parenting Study, with the exception of our exploratory findings regarding decreased reactivity in the precentral and postcentral gyrus during exclusion by strangers in abusive parents, it was quite remarkable that we did not find neural correlates of abusing or neglecting parenting behavior. While neural alterations following experienced child maltreatment have been repeatedly found in several populations, linking such brain changes to brain function and future behavior seems to be more complex (e.g., Teicher, Samson, Anderson, & Ohashi, 2016). Moreover, mixed findings are reported on the direction of structural and functional correlations (Kim et al., 2016). There are some promising studies however, that have detected associations between individual differences in parenting behavior and neural responses (including functional reactivity and connectivity) to infant stimuli (e.g., Atzil, Hendler, & Feldman, 2011; 2014; Musser, Kaiser-Laurent, & Ablow, 2012; Wan et al., 2014). However, those studies are mostly focused on parenting behavior in general or on positive parenting in particular. More research is needed to gain more insight into the neural correlates of abusing and neglecting parenting behavior.

THE CYCLE OF MALTREATMENT

While we found neural correlates of experienced abuse and neglect in our studies (Chapter 3, 4 and 5), those neural correlates were not associated with abusing or neglecting parenting behavior. Hence, no indications were found for a role of hippocampal volume or the neural correlates of threat processing (neural reactivity to emotional faces and social rejection) in ITCM in the current studies.

On a behavioral level, we observed intergenerational transmission of abuse in the 3G Parenting Study, whereas intergenerational transmission of neglect was not found. This was true for both the MRI subsamples of the 3G Parenting Study (see Chapter 3, 4, and 5) as well as for the complete 3G Parenting Study sample (n = 395; Buisman et al., 2020). Whereas intergenerational transmission of abuse was consistently found independent of the informant, transmission of neglect was only found using the perspective and data of a single informant. Self-reported experienced neglect was associated with self-reported perpetrated neglect, but intergenerational transmission of neglect was not found when using the multi-informant approach, where reports of different informants from each generation were combined (Buisman et al., 2020). This calls the validity of intergenerational transmission of neglect into question. The use of single-informant versus multi-informant approaches to measure child maltreatment is addressed into more detail in the dissertation of Buisman (2020). In the current papers the multi-informant approach was chosen

to increase validity by reducing random error and systematic bias (Thornberry, Knight, & Lovegrove, 2012).

While our findings confirm intergenerational transmission of abuse, fortunately, many maltreated parents do not transmit maltreating behavior towards their own children. However, it is very important to always be aware of the possible detrimental impact of maltreatment experiences on parenting behavior in clinical practice. Next to evidence for transmission of maltreatment, other studies indicate that experiencing child maltreatment might impact future parenting behavior in more nuanced ways (Van Wert et al., 2019). Maltreated parents might find it challenging to cope with daily stressors because of the long-lasting impact of maltreatment experiences on their biological stress system (Boivin & Hertzman, 2012). As a result, these parents may experience more difficulties to manage feelings of anger or frustration and meet the basic psychological and physical needs of their offspring. They might engage in suboptimal parenting behavior that does not necessarily meet the threshold to be labeled as maltreatment but might still be disadvantageous to the development of their offspring. It is therefore important to raise awareness about the possible destructive consequences of child maltreatment on a spectrum ranging from subtle to very distinct.

LIMITATIONS

The studies presented in this dissertation are not without limitations. A first limitation of our research is that we did not include a measure of all experienced stressful and potentially traumatic events. This would be recommended for future studies since the effects of trauma are suggested to be cumulative across the lifespan (Feder et al., 2016). Moreover, we have no information about the exact timing of the reported experienced events (including child abuse and neglect), whereas previous research shows that the timing of the experience might be important for the outcomes. For instance, early victimization has been associated with enhanced risk for developing PTSD (Lilly & Valdez, 2012) and a higher risk for subsequent revictimization later in life (Arata, 1999; Cloitre, Tardiff, Marzuk, Leon, & Portera, 1996).

Next, the experience of potentially traumatic events (including child maltreatment) was measured retrospectively. Recall bias might have affected reports of childhood trauma in our study. On the one hand, a recent meta-analysis reports poor agreement between prospective and retrospective measures of childhood maltreatment (Baldwin, Reuben, Newbury, & Danese, 2019). On the other hand, previous research shows that retrospective reports of maltreatment are verifiable (Chu, Frey, Ganzel, & Matthews, 1999) and suggest consistency between retrospective reports and prospective designs (Fergusson, Horwood, & Boden, 2011; Scott, McLaughlin, Smith, & Ellis, 2012). Furthermore, reporting bias due to

current psychopathology seems minimal (e.g., Hardt and Rutter, 2004; Scott et al., 2012). Moreover, we combined parent and child reports in the maltreatment scores in the 3G Parenting Study whenever possible to reduce individual bias.

It must also be noted that the correlational design of our research precludes drawing conclusions about causality. A prospective study following three generations would be recommended for future research to tackle those issues, although possibilities to conduct such a study may be limited. Another limitation of the 3G Parenting Study is the fact that we had less statistical power (i.e., smaller sample size) to examine the effects of perpetrated maltreatment than the effects of experienced maltreatment, since not all participants were parents. It would be recommended for future research to include an even larger sample of parents to examine the possibility that our results regarding maltreating parenting behavior are (partly) due to our relatively small sample.

Lastly, our findings may be partly attributable to task design. For instance, it might be that our Emotional Faces task was not sensitive enough to detect all neural alterations related to experienced and perpetrated child maltreatment. While setting up the 3G Parenting study our first intention was to make use of photos of actual family members of our participants, but unfortunately this turned out not to be feasible in the current design of the study. It is possible that faces of strangers are less evocative, impersonal elicitors of emotion for some individuals because of their lower emotional salience. Additionally, we presented unfamiliar adult faces to participants of both generations (offspring and their parents), whereas presenting pictures of children to parents might be more suitable while examining the family context.

FUTURE DIRECTIONS AND CLINICAL IMPLICATIONS

The impact of trauma

Our findings of Chapter 2 indicate that stressful (non-A1) life events that are not classified as traumatic, according to the DSM A1 criterion, can generate at least the same levels of PTSD symptom severity and suffering in daily functioning as A1 events. Hence, our findings call the clinical usefulness of the A1 criterion of PTSD into question. We therefore want to underscore the need to pay closer attention to PTSD symptom profiles rather than the strict definition of the A1 criterion. Since exposure to potential traumatic experiences in general, and stressful (non-A1) life events in particular, continues to be neglected in clinical practice (e.g., Gottlieb, Poyato, Valiente, Perdigon, & Vazquez, 2018), it is important to raise awareness of the impact of potentially traumatic and stressful life events and be especially aware of high levels of avoidance in men after non-A1 stressful life events. We want to stress the need to recognize the potential impact of interpersonal stress in particular, which is often not recognized in clinical practice (Mauritz et al., 2013). Many clinicians

report hesitancy to pay attention to past potentially traumatic experiences because they believe this might trigger higher levels of distress and impairment. It is important to note that there is no evidence for this persuasion (Cusack, Grubaugh, Knapp, & Frueh, 2006; Griffin, Resick, Waldrop, & Mechanic, 2003). Improved recognition of potentially traumatic experiences is needed to provide adequate treatment in clinical practice (Cusack et al., 2006; Mueser et al., 2004; Van den Berg & Van der Gaag, 2012).

Moreover, it is vital to give safety assessments a more prominent role in clinical and medical practice, for instance by including a safety checklist like the Licht Instrument Risico-Inschatting Kindveiligheid (LIRIK; Ten Berge & Eijgenraam, 2009) within the intake procedure. The solution-oriented approach Signs of Safety includes scale questions that can be used among professionals as well as during conversation with both parents and children to supplement the safety check (Turnell & Edwards, 1999; Turnell & Essex, 2006). Additionally, professionals should take their gut feelings serious and discuss them with colleagues. Furthermore, trauma exposure should receive more attention in academic research as well since trauma, and child maltreatment in particular, has been suggested as an important unrecognized confounder, especially in many psychiatric neuroimaging research (Teicher et al., 2018).

Zooming in on child maltreatment, our differential findings regarding child abuse versus neglect are consistent with studies showing that specific types of maltreatment seem to selectively affect sensory systems and neural pathways that process stressful and traumatic incidents (Teicher & Samson, 2016) and highlights the importance of distinguishing between abuse and neglect in both future research and clinical practice. Our findings emphasize that type of maltreatment matters and raise concerns about the alternative approach of counting up adverse childhood experiences to provide a simple composite score. Treating maltreatment as a homogenous concept masks important differences and associated sequelae.

Moreover, the impact of child neglect in particular should not be underestimated, since the outcomes can be at least as severe as the outcomes of child abuse. While more and more researchers agree on the devastating consequences of child neglect, it is striking that neglect is still the least studied form of early-life adversity (Lippard & Nemeroff, 2020). This is partly because emotional abuse and neglect are least likely to come to attention in medical and clinical practice, because it does not always result in visible physical injuries (in the case of emotional neglect). Moreover, since neglect represents the absence of behavior instead of the presence of behavior (as in the case of abuse) it requires a judgment whether the behavior in question should have been present. This makes neglect a more abstract construct that is more difficult to assess, both for victims and for their environment such as family and friends, teachers, clinical therapists and medical staff. However, since emotional and physical neglect are the most prevalent types of maltreatment and because of its long-lasting adverse consequences, more research on the issue of neglect

is urgently needed. Furthermore, it is warranted to increase awareness of the impact of neglect, not only through academic research, but also by educating staff members of clinical practices, schools, hospitals and other relevant organizations.

For future studies it could also be informative to further distinguish between different subtypes of child abuse and neglect (such as emotional and physical abuse and emotional and physical neglect) as some studies indicate that these different subtypes may affect emotional processing and associated outcomes in general differently (e.g., Carr, Martins, Stingel, Lemgruber, & Juruena, 2013; Doretto & Scivoletto, 2018). A possible explanation might be that different subtypes of maltreatment exposure involve differential exposure to a range of emotional facial expressions and behavior of maltreating parents possibly inducing specific neural specialization for emotion processing. For the 3G Parenting Study we initially aimed to distinguish between the effects of the emotional and physical subtypes of abuse and neglect. However, internal consistencies for CTQ items on physical neglect were not sufficient and the physical abuse and physical neglect scale were both highly skewed to the right (see Buisman et al., 2020). We therefore decided to combine the physical and emotional scales. Research outcomes on the impact of maltreatment subtypes are inconsistent, probably partially because of high rates of co-occurrence of maltreatment subtypes and diversity in methodological and statistical methods and comparison groups (e.g., Doretto & Scivoletto, 2018; Manly, Kim, Rogosch, & Cicchetti, 2001; Nolin & Ethier, 2007; Petrenko, Friend, Garrido, Taussig, & Culhane, 2012). Although high rates of co-occurrence of maltreatment subtypes make it more difficult to pull apart the possible differential impact of those subtypes, we encourage future researchers to attempt to provide more clarity on this topic. More information on subtype differences is relevant for clinical practice since it may help to tailor treatment and increase the effectiveness of therapeutic strategies to reduce the impact of maltreatment.

Moderating factors

Our findings emphasize the need to take gender effects into account when examining the impact of trauma and stress on different levels, both in academic research and in clinical practice. On a behavioral level, in men PTSD symptoms were more severe after non-A1 than A1 events, whereas in women symptoms were equally severe after non-A1 and A1 events (Chapter 2). On a neural level, we found associations between experienced child abuse and reduced hippocampal volume, only in men (Chapter 3). Consideration of gender effects might also help explain seemingly contradictory findings in previous studies. Moreover, it is recommended for future research to examine the mechanisms behind gender differences regarding the impact of trauma into more detail, because it may inform the development of gender-sensitive recommendations for assessment and treatment in clinical practice.

Furthermore, whereas most trauma studies so far made use of a cross-sectional design, longitudinal research on the impact of trauma begins to emerge (Busso et al., 2017; Opel et al., 2019; Swartz et al., 2015). More longitudinal studies regarding the impact of trauma (including child maltreatment) and underlying neurobiology are vital to detect modifiable targets for preventive and early interventions.

More research is also warranted to identify genes and SNPs associated with neurobiological vulnerability following child maltreatment. Genetic imaging studies are evolving and suggest gene-environment interactions on structural and functional alterations after experiencing child maltreatment (Lippard & Nemeroff, 2020). Epigenetics might also be involved as a mechanism in ITCM (Braun & Champagne, 2014; Galler & Rabinowitz, 2014; Gudsnuk & Champagne, 2012) and should be further examined. Genetic variation might connect child maltreatment, neurobiology and vulnerability for damaging outcomes (Lippard & Nemeroff, 2020). For instance, some individuals might be more vulnerable to detrimental effects of child maltreatment because of a genetic predisposition for psychopathology.

Moreover, it is recommended to study the characteristics and experience of different potentially traumatic events into more detail, also in relation to gender differences. Previous research often fails to sufficiently capture the heterogeneity of the concept of maltreatment, including the nature of the maltreatment experience (e.g., age of onset, developmental period during which the maltreatment occurs, duration, severity) and characteristics of the victims and perpetrators (e.g., age, gender, neurobiological factors, coping strategies, other potentially traumatic experiences). Gaining more insight into the diversity of individual experiences will improve efforts to effectively respond to the unique needs and deficits of maltreated children and their parents.

Paradigm design

Results of previous studies suggest that adults are distinctively attuned to social-emotional signals from infant faces (Parsons, Young, Kumari, Stein, & Kringelbach, 2011; Thompson-Booth, et al. 2014). Faces of children elicit stronger activation in several brain regions (e.g., the amygdala, fusiform gyrus and pre- and postcentral gyri) compared to adults' faces in parents (Luo et al., 2015). Moreover, infant-specific face processing deficits are found in neglectful mothers, although more generic effects (for infant and adult faces) were also reported (León et al., 2019). Some previous studies presented idiosyncratic stimuli of one's own offspring that specifically activate attachment representations in parents and found evidence for different neural substrates of processing such familiar and personally salient stimuli (e.g., Barrett et al., 2012; Barrett & Flaming, 2011; Kluczniok et al., 2017; Leibenluft, Gobbini, Harrison, & Haxby, 2004; Nitschke et al., 2004; Strathearn & Kim, 2013; Strathearn, Li, Fonagy, & Montague, 2008). That is, stimuli related to one's own offspring activate neural regions implicated in parenting behavior and related systems

such as affect, reward and executive functions (Barrett & Flaming, 2011). Moreover, altered neural correlates of emotional face processing for known vs. unknown faces are found in association with experienced maltreatment (Neukel et al., 2019) and parenting behavior (Atzil et al., 2011; Barrett & Fleming, 2011; Musser et al., 2012; Wan et al., 2014). For future studies we therefore recommend to include pictures or movie clips of both familiar (offspring for parents and vice versa) and unfamiliar faces to further investigate whether child maltreatment is predominantly associated with altered processing of emotions in the family context, although this would decrease standardization of the Emotional Faces task. Likewise, in our Cyberball paradigm names of family members were used as stimuli. As mentioned above, pictures or movie clips of own offspring and parents might be more powerful to detect neural alterations related to child maltreatment in future studies.

Although a general implicit check for attention to the emotional faces was included within our Emotional Faces Task by requiring participants to attend to the gender of the face, it might be interesting to examine the direction of attention during the Emotional Faces task into more detail. It might be that maltreated individuals avoid the processing of emotional information by quickly redirecting their attention. Attentional bias away from threat cues is associated with severity of maltreatment experiences (Pine et al., 2005). This might also be related to age since maltreatment exposure and severity were related to attentional bias toward threat in children versus away from threat in adolescents (Weissman et al., 2019), which might partly explain our interaction effects with age. Eye tracking research in the MRI scanner might be useful to investigate this hypothesis.

Connectivity

The neuroimaging studies in this dissertation focused on several isolated neural regions. These regions (such as the amygdala and PFC) are known to be structurally and functionally connected (Davidson & Irwin, 1999). As emotions and behavior are known as the output of complex interactions within and between specialized neural networks, future research may benefit from examining the brain as a network of interconnected regions. To date, only a few studies reported altered neural network architecture associated with experienced child maltreatment and investigated structural neural networks related to maltreatment (Ohashi et al., 2019; Teicher, Anderson, Ohashi, & Polcari, 2014). Connectivity within frontolimbic circuits has been associated with efficient emotion regulation (Kim, Gee, Loucks, Davis, & Whalen, 2011; Phillips, Ladouceur, & Drevets, 2008) and altered connectivity in this network was found in maltreated individuals, at rest (Herringa et al., 2013) and during emotional face processing tasks (Demers et al., 2018; Fonzo et al., 2013; Jedd et al., 2015). This may suggest the presence of an inefficient regulatory system in maltreated individuals. Moreover, a structural connectivity study found that altered inferior fronto-temporal-occipital connectivity, which is associated with emotional visual processing, in neglectful mothers might play a role in intergenerational transmission of neglect

(Rodrigo et al., 2016). Examining both functional and structural connectivity between regulatory brain regions (e.g., PFC) and regions involved in emotional processing (e.g., the amygdala) can advance our understanding of the potential mechanisms underlying ITCM. Furthermore, developmental patterns in connectivity (e.g., as was found for amygdala connectivity) have not been investigated in association with childhood trauma specifically (Weissman et al., 2019), but might play a role in the explanation of the age effects that were reported in this dissertation.

Resilience

It is important to point out that despite clear associations between early adversity and problematic outcomes later on, many individuals who experience trauma have the capacity for resilient outcomes in one or more domains including positive educational, social, emotional, behavioral and occupational outcomes (Cicchetti, Rogosch, Lynch, & Holt, 1993; Demers et al., 2018; Norbury, Perez-Rodriguez, & Feder, 2019). Potentially traumatic events are highly prevalent and most people who experience such events recover (Tolin & Foa, 2008). In our NESDA sample, 70% of women and 85% of men of the A1 event group did not meet PTSD B, C and D criteria versus 72% of women and 69% of men in the non-A1 event group (Chapter 2). Zooming in on child maltreatment, a review of resilience studies estimates that 10-25% of maltreated children achieves resilience on an emotional, educational and behavioral level (Walsh, Dawson, & Mattingly, 2010). Moreover, research indicates that 70% of maltreated parents do not transmit maltreatment to their own offspring. This suggests that there are numerous factors that might protect from aversive outcomes after experiencing traumatic events. However, a lot is still unknown about why some individuals show resilience after trauma and others do not (e.g., Ásgeirsdóttir et al., 2018). More research is warranted to gain more insight into this resiliency, instead of only focusing on the mechanisms playing a role in aversive outcomes.

On a behavioral level, a meta-analysis by Schofield and colleagues (2013) found that stable, safe and supporting relationships with parents, siblings, and intimate partners in adulthood play a role in protecting against ITCM. Moreover, a few promising results are also reported on a neural level. A recent review reports preliminary evidence for possible functional and structural neural mechanisms of resilience after childhood trauma, including increased hippocampal volume, lower hippocampal reactivity to emotional faces and heightened amygdala habituation to stress (Moreno-López et al., 2019). Moreover, altered frontal brain reactivity and connectivity in resilient trauma-exposed individuals compared to vulnerable trauma-exposed and non-trauma-exposed individuals is found (Demers et al., 2018; New et al., 2009; Van der Werff et al., 2013), suggesting neural correlates of emotion processing between maltreated and non-maltreated individuals might also differ based on current adaptive functioning.

However, research on the neural substrates of resilience after trauma is still scarce and further study of resilient processes after trauma exposure throughout development is warranted, because it may reveal novel intervention targets to preferably prevent or otherwise treat damaging outcomes of trauma. Moreover, while most previous resilience studies are focused on the absence or presence of psychopathology after experienced trauma, future studies should focus on resilient functioning across emotional, cognitive and social domains and include the investigation of possible gender effects. Since resilience-promoting factors interact, it is crucial to study these factors in the context of each other instead of in isolation. Longitudinal designs would be preferred, because of the dynamic nature of the concept of resilience concerning active adaptation after the experience of adversity (e.g., Kalisch et al., 2019; Norbury et al., 2019; Rutter, 2012). Longitudinal studies might also provide more knowledge about whether neurobiological substrates of resilience denote adaptations after trauma or represent preexisting characteristics.

Furthermore, it is recommended to put more focus on strengths, resources and protective factors in clinical practice instead of solely focusing on the experienced trauma itself, psychological symptoms and risk factors. This is consistent with a solution-focused (brief) therapy, a form of counseling aimed at reinforcing individuals' own autonomy and strengths and identifying pre-existing skills to help find solutions for problems (Bakker & Bannink, 2008; Berg, 1994; De Shazer et al., 1986). Although evaluation of this approach is in its infancy and future studies are needed, a review of previous studies provides initial evidence for effectiveness of solution-focused therapy for trauma-exposed patients (Eads & Lee, 2019). It is also embedded in the family psychiatry field by professionals who are working with multiproblem families who are at higher risk for child maltreatment.

CONCLUSION

In this dissertation we examined the impact of different types of stressful and traumatic events on the mind and the brain. The role of structural and functional neural correlates of threat processing in ITCM was examined for the first time using a family study design. Our findings show that hippocampal volume and neural reactivity to emotional faces and social rejection is associated with experienced maltreatment but not with maltreating behavior. Hence, no neural mechanisms could be identified that are involved in ITCM. While exploratory analyses suggest that abusive parents show lower reactivity in the precentral and postcentral gyrus during exclusion by strangers, our other two neuroimaging studies found no neural correlates of abusing or neglecting parenting behavior. To date, research on the neural correlates of maltreating parenting behavior is scarce (Van IJzendoorn et al., 2020). Further research into any neural mechanisms that might play a role in intergenerational transmission of abuse and neglect is vital for the design and implementation of

effective preventive interventions. Although there is still a long way to go, neuroimaging studies on the impact of trauma contribute to the development of imaging-informed interventions including brain stimulation, targeted neurofeedback and cognitive-emotional training (Norbury et al., 2019). Some of those interventions are already starting to get implemented in real-life settings (Greenberg, 2006; Keynan et al., 2019; Waugh & Koster, 2015).

This dissertation also highlights the importance to distinguish between different types of maltreatment (abuse and neglect) in research and clinical practice and suggests that the impact of experiencing rejection and maltreatment by your own parents goes beyond the family context. It is crucial to raise awareness regarding the detrimental impact of stressful life events that are not classified as traumatic according to the DSM A1 criterion, and child neglect in particular, since outcomes can be at least as severe as the outcomes of A1 traumatic events such as child abuse. Our findings shed a new light on the clinical usefulness of the A1 criterion and the role of gender in the impact of trauma.

To date, several parenting intervention programs have been developed to enhance parental sensitivity and the quality of parent-child interaction with the aim of reducing ITCM (Madigan et al., 2019). However, while some studies show promising results (e.g., Chaffin et al., 2004; Kim et al., 2016), a meta-analysis including 20 intervention programs shows that only 5 out of 20 of the studied intervention programs effectively prevented or reduced the risk of child maltreatment (Euser, Alink, Stoltenborgh, Bakermans-Kranenburg, & Van IJzendoorn, 2015). More research into the impact of trauma and mechanisms of ITCM utilizing longitudinal designs is vital to decrease the impact of trauma and prevent child maltreatment. Importantly, nature and nurture should not be considered in isolation, because they are known to interact in shaping developmental outcomes of trauma. Studying those mechanisms will bring the field closer to early detection of aetiological factors related to child maltreatment. Increasing insight into modifiable targets should ultimately provide improved prevention and the development of more effective intervention strategies. Bridging the gap between science and clinical practice is essential to ultimately break the cycle of child maltreatment.

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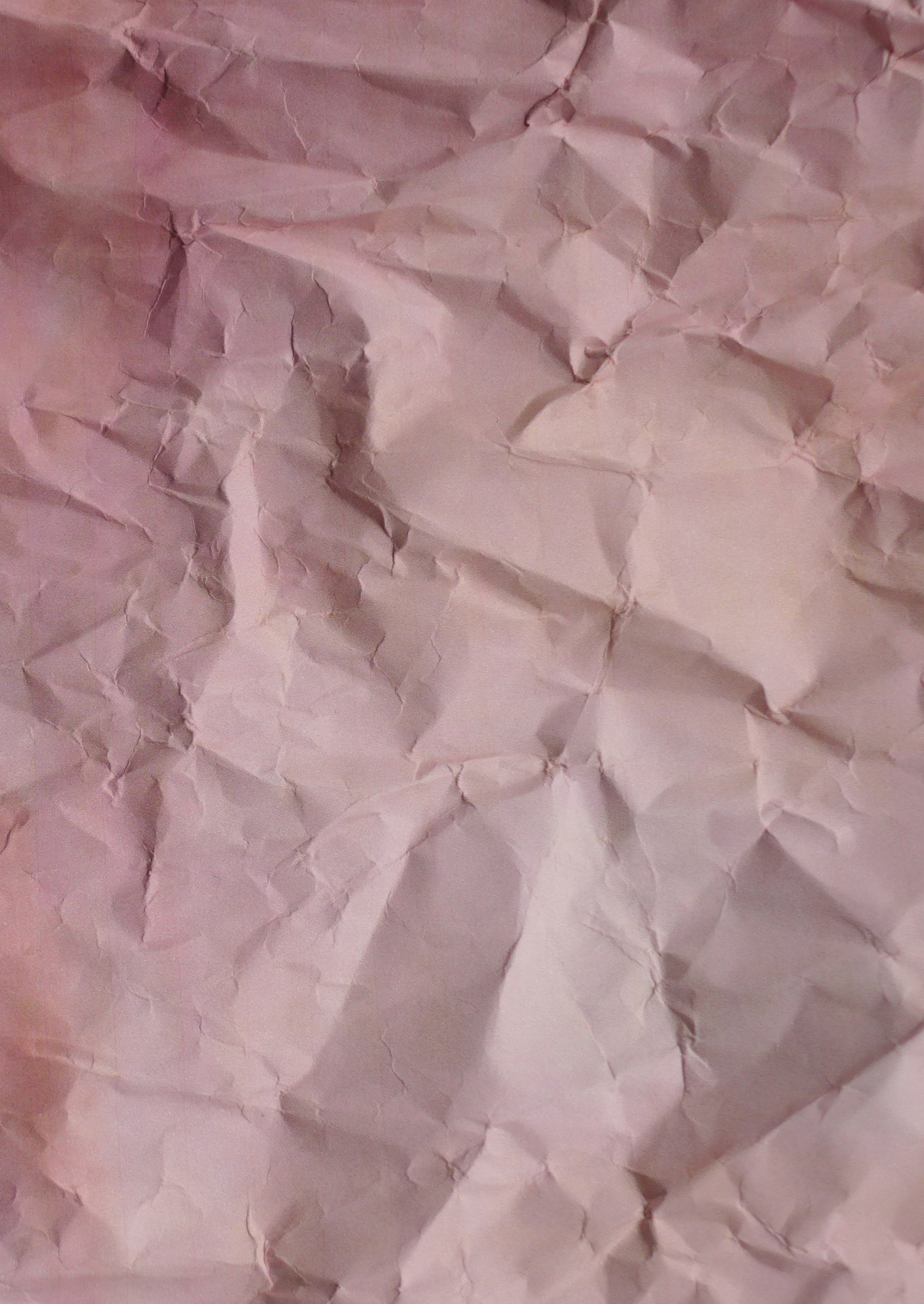
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Chapter 7

Appendices

NEDERLANDSE SAMENVATTING (DUTCH SUMMARY)

Meer dan de helft (60-90%) van alle mensen maakt een potentieel traumatische gebeurtenis mee in zijn of haar leven (Kessler et al., 2017; Kilpatrick et al., 2013; Thordardottir et al., 2015). Stress en trauma kunnen langdurige schadelijke gevolgen hebben met betrekking tot emotioneel, psychologisch en fysiek welzijn. Zo is ernstige of chronische stress na een traumatische gebeurtenis in verband gebracht met het ontwikkelen van fysieke en psychologische stoornissen zoals hart- en vaatziekten, angststoornissen, posttraumatische stressstoornis (PTSS) en depressie (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), hetgeen samenhangt met vele uitdagingen tijdens de rest van het leven (Van der Werff, Van den Berg, Pannekoek, Elzinga, & Van der Wee, 2013). Vanwege de hoge prevalentie en potentieel schadelijke effecten is stress bestempeld als de "Gezondheidsepidemie van de 21e eeuw" (WHO, 2013). Het doel van dit proefschrift was om de impact van verschillende typen traumatische en stressvolle levensgebeurtenissen te onderzoeken, met een focus op de rol van het brein in de intergenerationele overdracht van kindermishandeling en verwaarlozing.

Traumatische versus stressvolle gebeurtenissen

Sommige stressvolle gebeurtenissen kunnen traumatisch zijn. PTSS is één van de weinige stoornissen in de DSM (American Psychiatric Association, 2013) die een etiologische factor vereist om de diagnose te kunnen stellen, namelijk het meemaken van een traumatische gebeurtenis. Dit A1 criterium van PTSS wordt in de DSM-5 als volgt omschreven: 'blootstelling aan een feitelijke of dreigende dood, ernstige verwonding of seksueel geweld'. Dit betekent dat gebeurtenissen zoals het onverwacht overlijden van een familielid of een goede vriend door een natuurlijke oorzaak, of emotionele verwaarlozing niet voldoen aan dit criterium van PTSS. De afgelopen jaren is er een debat gaande over de validiteit en bruikbaarheid van dit A1 criterium. Verschillende studies hebben namelijk aangetoond dat andere stressvolle (niet-A1) levensgebeurtenissen een vergelijkbaar of zelfs een hoger niveau van PTSS-symptomen kunnen veroorzaken dan formele A1 gebeurtenissen (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). Dit benadrukt het belang van een hernieuwde discussie over de rol van stressvolle (niet-A1) levensgebeurtenissen bij de ontwikkeling van PTSS. In **Hoofdstuk 2** van dit proefschrift hebben we daarom in een groot, voornamelijk klinisch sample (n = 1433) uit de Nederlandse Studie naar Depressie en Angst (NESDA) onderzocht of formele DSM-IV-TR traumatische (A1) en stressvolle (niet-A1) gebeurtenissen verschillen met betrekking tot PTSS-symptoomprofielen. Om blootstelling aan A1 en niet-A1 gebeurtenissen te meten

is gebruik gemaakt van de Life Events Checklist (LEC; Weathers, Keane, & Davidson, 2001) en de PTSS Symptoom Schaal - Interview Versie (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993). Participanten beschreven de meest vervelende gebeurtenis die ze ooit hadden meegemaakt en werden aan de hand van deze zogenoemde indexgebeurtenis toegewezen aan de A1 of niet-A1 groep.

In **Hoofdstuk 2** hebben we tevens onderzocht of potentiële sekseverschillen invloed hebben op PTSS-symptomatologie na A1 en niet-A1 gebeurtenissen. Uit eerder onderzoek weten we dat vrouwen ongeveer tweemaal zoveel kans hebben om PTSS te ontwikkelen als mannen, ook al is de kans dat vrouwen een A1 traumatische gebeurtenis meemaken kleiner (Olff, Langeland, Draijer, & Gersons, 2007; Tolin & Foa, 2008). Mannen en vrouwen maken verschillende type A1 gebeurtenissen mee, maar zelfs wanneer daarvoor wordt gecontroleerd blijft het verschil in PTSS-prevalentie tussen mannen en vrouwen bestaan (Christiansen & Hansen, 2015; Moser, Hajcak, Simons, & Foa, 2007; Tolin & Foa, 2008). Het is onduidelijk of deze verhoogde kwetsbaarheid bij vrouwen om PTSS te ontwikkelen na het ervaren van A1 gebeurtenissen ook geldt voor niet-A1 gebeurtenissen. Bovendien is er nog weinig kennis over de mechanismen die sekseverschillen in PTSS-ontwikkeling kunnen verklaren. Een belangrijk doel van onze studie was daarom om te onderzoeken of het verband tussen type gebeurtenis (A1 versus niet-A1) en PTSS-symptomen verschillend is voor mannen en vrouwen. Tot slot hebben we getracht een verklarend mechanisme voor deze potentiële sekseverschillen te ontdekken door te onderzoeken of angst en subjectieve ervaring van de meegemaakte (index)gebeurtenis een rol spelen bij deze sekseverschillen.

Onze resultaten in **Hoofdstuk 2** lieten zien dat PTSS-symptomen in de groep participanten die een niet-A1 gebeurtenis heeft meegemaakt (niet-A1 groep) even ernstig of zelfs ernstiger waren dan in de groep participanten die een A1 gebeurtenis heeft meegemaakt (A1 groep). Van de niet-A1 groep rapporteerde 86% PTSS-symptomen als intrusies, vermijding en/of verhoogde spanning gerelateerd aan de indexgebeurtenis tijdens de afgelopen vijf jaar versus 50% van de A1 groep. Opmerkelijk is dat voor mannen de PTSS-symptomen ernstiger waren na niet-A1 dan na A1 gebeurtenissen (voornamelijk wat betreft vermijding en spanningsgerelateerde symptomen), terwijl bij vrouwen de PTSS-symptomen even ernstig waren na niet-A1 en A1 gebeurtenissen. Hoewel vrouwen een significant hoger niveau van PTSS-symptomen rapporteerden na A1 gebeurtenissen dan mannen (29.9% versus 15.4% voldeed aan PTSS-criteria), was er geen verschil tussen mannen en vrouwen na niet-A1 gebeurtenissen (vrouwen: 28.2%; mannen: 31.3%). Bovendien was het niveau van angst en ervaren invloed van de gebeurtenis hoger bij vrouwen dan bij mannen. De mate van angst en ervaren invloed van de gebeurtenis na A1 gebeurtenissen hing voor vrouwen sterker samen met PTSS-symptomen dan voor mannen, maar dit was niet het geval na niet-A1 gebeurtenissen. Dit wijst erop dat verschillende psychologische processen een rol kunnen spelen bij de ontwikkeling van PTSS-symptomen na niet-A1 en A1 ge-

beurtenissen bij mannen en vrouwen. De opvallend hoge mate van vermijding na niet-A1 gebeurtenissen in vergelijking tot A1 gebeurtenissen die in onze studie bij mannen werd gevonden zou hierbij een rol kunnen spelen. Mogelijk vertonen mannen na het meemaken van een niet-A1 gebeurtenis meer vermijding omdat het minder sociaal geaccepteerd is voor mannen om op negatieve wijze te worden beïnvloed door gebeurtenissen die niet officieel als traumatisch zijn geclassificeerd. Meer onderzoek is nodig om mechanismen die een rol spelen bij sekseverschillen in PTSS te ontrafelen.

Wanneer we inzoomden op de gerapporteerde niet-A1 gebeurtenissen in onze studie viel op dat voor zowel mannen als vrouwen ernstige lichamelijke ziekten (van jezelf of een naaste), relationele problemen en het overlijden van een naaste tot de meest gerapporteerde niet-A1 indexgebeurtenissen behoorden. Dit komt overeen met eerder onderzoek (e.g., Mol et al., 2005; Roberts et al., 2012) en zou erop kunnen wijzen dat interpersoonlijke, relationele gebeurtenissen het hoogste niveau van stress veroorzaken en daarmee de grootste voorspeller voor het ontwikkelen van PTSS-symptomen zijn.

Samengevat lieten onze resultaten uit **Hoofdstuk 2** zien dat stressvolle (niet-A1) levensgebeurtenissen die volgens de DSM niet als traumatisch worden geclassificeerd geassocieerd waren met minimaal eenzelfde niveau van PTSS-symptomen en lijden in het dagelijks leven als formele A1 traumatische gebeurtenissen. Terwijl vrouwen vergelijkbare niveaus van PTSS-symptomen lieten zien na beide typen gebeurtenissen (A1 en niet-A1), rapporteerden mannen zelfs hogere niveaus van PTSS-symptomen na niet-A1 gebeurtenissen dan na A1 gebeurtenissen. Deze bevindingen laten zien dat mannen en vrouwen verschillend reageren op stressvolle en traumatische gebeurtenissen, en signaleren een belangrijke negatieve consequentie van het A1 criterium van PTSS zoals gehanteerd in de DSM. Aan de hand van deze resultaten adviseren wij clinici om meer aandacht te besteden aan PTSS-symptoomprofielen in plaats van de strikte definitie van het A1 criterium uit de DSM aan te houden, om zo te voorkomen dat cliënten met symptomen uitgesloten worden van behandeling (c.q. vergoeding van deze behandeling). Aangezien stressvolle (niet-A1) levensgebeurtenissen veel voorkomen, zou het identificeren van factoren die mogelijk verband houden met een relatief goede aanpassing aan deze gebeurtenissen de samenleving veerkrachtiger kunnen maken en stress en lijden in het dagelijks leven kunnen verminderen of zelfs voorkomen. Meer onderzoek naar de mechanismen achter sekseverschillen in PTSS is belangrijk omdat dit richting zou kunnen geven aan het ontwikkelen van preventieve therapeutische interventies in de klinische praktijk.

Intergenerationele overdracht van kindermishandeling (IOKM)

Eerder onderzoek laat ons zien dat het meemaken van stressvolle en traumatische levensgebeurtenissen tijdens de kindertijd sterker samenhangt met het ontwikkelen van psychopathologie dan het meemaken van negatieve levensgebeurtenissen later in het leven (e.g., Spinhoven et al., 2010), onder andere omdat deze vaak plaatsvinden binnen

de familiaire context. Wereldwijd wordt meer dan 50% van alle kinderen blootgesteld aan (potentieel traumatische) stress (Fenoglio, Brunson, & Ampam, 2006). Het meemaken van stressvolle en potentieel traumatische gebeurtenissen tijdens de kindertijd wordt geassocieerd met een verhoogd risico op langdurige gedragsproblemen, fysieke en mentale gezondheidsproblemen (e.g., Heim, Shugart, Craighead, & Nemeroff, 2010; McCrory, De Brito, & Viding, 2011a; Norman et al., 2012; Spinhoven, Penninx, Van Hemert, De Rooij, & Elzinga, 2014; Twardosz & Lutzker, 2010) en heeft een negatieve invloed op sociaal en cognitief functioneren en economische productiviteit (e.g., Currie & Spatz Widom, 2010; Lansford et al., 2002; Shirtcliff et al., 2009). Bovendien is stress en trauma in de kindertijd in verband gebracht met structurele en functionele veranderingen in het brein, zelfs decennia later (e.g., Dannlowski et al., 2012, Teicher et al., 2003). In **Hoofdstuk 3, 4 en 5** van dit proefschrift lag de focus op het onderzoeken van deze neurobiologische impact van trauma waarbij we ons richtten op één van de meest voorkomende vormen van trauma tijdens de kindertijd, namelijk kindermishandeling en verwaarlozing (Martins, De Carvalho Tofoli, Von Werne Baes, & Juruena, 2011).

In Nederland waren in 2017 tussen de 89.160 en 127.190 kinderen slachtoffer van minimaal één vorm van mishandeling (Van Berkel, Prevoo, Linting, Pannebakker, & Alink, 2020). De negatieve gevolgen van het meemaken van kindermishandeling op de psychologische, sociale en biologische ontwikkeling zijn groot en kunnen de rest van het leven aanhouden (e.g., McCrory et al., 2011a; Norman et al., 2012). Het is daarom van essentieel belang om kennis over de impact van kindermishandeling op verschillende niveaus (o.a. op neuraal, cognitief en gedragsmatig niveau) te vergroten om zo potentiële doelen voor preventieve therapeutische interventies in de toekomst te identificeren. In **Hoofdstuk 3, 4 en 5** hebben we ons gericht op het onderzoeken van de neurale correlaten van één van de meest opvallende gevolgen van kindermishandeling, namelijk het verhoogde risico op mishandeling van eigen kinderen (Dubowitz et al., 2001; Madigan et al., 2019; Pears & Capaldi, 2001; Savage, Tarabulsy, Pearson, Collin-Vézina, & Gagné, 2019; Van IJzendoorn, Bakermans-Kranenburg, Coughlan, & Reijman, 2020). Ongeveer 30% van alle ouders die zelf mishandeld zijn in de kindertijd mishandelt zijn of haar eigen kinderen, terwijl dit percentage significant lager ligt voor ouders die zelf geen kindermishandeling hebben meegemaakt (e.g., Berlin, Appleyard, & Dodge, 2011; Dixon, Hamilton-Giachritsis, & Browne, 2005). Er wordt zelfs gesteld dat mishandelde ouders tweemaal zoveel kans hebben om hun eigen kinderen te mishandelen (Madigan et al., 2019; Van IJzendoorn et al., 2020). Er zijn in eerder onderzoek echter nog weinig verklarende mechanismen voor intergenerationele overdracht van kindermishandeling (IOKM) op adequate wijze onderzocht en/of bevestigd (Alink, Cyr, & Madigan, 2019). Om deze cirkel van intergenerationele overdracht van mishandeling en verwaarlozing te doorbreken en effectieve preventieve interventies in te kunnen zetten is het cruciaal om de mechanismen achter deze overdracht te ontrafelen.

De 3-Generatie Ouderschapsstudie

Om mechanismen die mogelijk een rol spelen bij de intergenerationele overdracht van emotieregulatie, stress en opvoedstijlen te onderzoeken op onder andere genetisch, fysiologisch, neuraal, cognitief en gedragsmatig niveau hebben we een grootschalige multigenerationele familiestudie opgezet: De 3-Generatie Ouderschapsstudie (3G Parenting Study; zie ook Buisman et al., 2020; Compier-de Block, 2017). Voor deze 3G Ouderschapsstudie hebben we participanten (zogenoemde 'targets') geïncludeerd met een verhoogd risico op meegemaakte kindermishandeling. Ons doel was om rondom deze targets zoveel mogelijk familieleden te includeren van drie (of meer) generaties, waaronder (groot)ouders, partners, kinderen, volwassen broers en zussen (en hun partners), neven, nichten en schoonouders (zie Figuur 1 Hoofdstuk 1). Gezinnen konden deelnemen aan onze studie als ten minste twee eerstegraads familieleden van minimaal 7,5 jaar of ouder van twee generaties bereid waren om deel te nemen. Afhankelijk van de familiesamenstelling hebben we participanten uitgenodigd voor één of twee familiebezoeken aan ons laboratorium. Volwassen participanten kwamen één keer naar het lab met hun eigen nucleaire familie (het gezin, met partner en kinderen) en éénmaal met hun gezin van herkomst (met volwassen broer(s) en/of zus(sen) en hun ouders). Tijdens deze bezoeken aan het lab hebben we verschillende vragenlijsten en computertaken afgenomen en hebben participanten deelgenomen aan verschillende interactietaken met hun familieleden. Tevens hebben wij haar- en speekselsamples verzameld om hormoonlevels en DNA te onderzoeken en hebben we hartslagvariabiliteit en huidgeleiding gemeten tijdens verschillende taken. Meegemaakte kindermishandeling werd gemeten met behulp van aangepaste versies van de Conflict Tactics Scale (CTS; Straus, Hamby, Finkelhor, Moore, & Runyan, 1998) bij participanten van alle generaties en mishandelend gedrag bij alle participanten met kinderen. In totaal hebben we in de 3G Ouderschapsstudie 395 participanten met een leeftijd van 7,5 tot 88 jaar geïncludeerd. Zij waren afkomstig uit 63 verschillende families.

Een belangrijk doel van de 3G Ouderschapsstudie was om de potentiële rol van het brein te onderzoeken in IOKM. Indien mogelijk werden participanten (ouders en hun kinderen) daarom tevens uitgenodigd om deel te nemen aan een fMRI sessie. Het fMRI sample van de 3G Ouderschapsstudie bestond uit 180 participanten afkomstig uit twee generaties van 53 families met een brede leeftijdsrange (8-70 jaar). Tijdens de fMRI sessie werden zowel structurele als functionele scans gemaakt van het brein in rust en terwijl participanten in de fMRI scanner onder andere een Emotionele Gezichtentaak uitvoerden en een sociale exclusietaak genaamd de Cyberball taak. Tijdens de Emotionele Gezichtentaak kregen participanten verschillende boze, angstige, verbaasde, vrolijke en neutrale gezichten te zien waarbij ze telkens moesten aangeven of er een man of een vrouw op de foto werd getoond. Tijdens de Cyberball taak speelden participanten twee rondes van een virtueel balspel met twee andere spelers (die door de computer werden gecontroleerd). Alle participanten speelden een ronde van het spel met twee onbekenden (onbekende

ronde) en een andere ronde met een familielid en een onbekende (bekende ronde). Voor kinderen was dit familielid hun eigen moeder en ouders speelden met hun oudste kind (deelnemend aan de 3G Ouderschapsstudie). Elke ronde begon met een inclusieblok waarbij de participant in een eerlijk aantal gevallen de bal toegespeeld kreeg van de andere spelers. De participant kon de bal vervolgens teruggooien naar een andere speler. Daarna volgde een sociaal exclusieblok met dezelfde spelers waarbij de participant de bal nog één keer kreeg toegespeeld en daarna helemaal niet meer.

IOKM en hippocampaal volume

De 3G Ouderschapsstudie is opgezet om mechanismen die mogelijk een rol spelen bij IOKM te onderzoeken op verschillende niveaus. **Hoofdstuk 3, 4 en 5** van dit proefschrift hebben betrekking op de neurale correlaten van IOKM, oftewel de rol van het brein in IOKM. Onderzoek laat zien dat het meemaken van kindermishandeling van invloed is op de structuur en functie van het brein in hersengebieden die onderdeel uitmaken van het limbisch systeem, waaronder de hippocampus (e.g., Teicher et al., 2003) en prefrontale cortex. De hippocampus staat bekend als één van de meest plastische en stress-sensitieve hersengebieden (e.g., Teicher et al., 2018) en speelt een belangrijke rol bij leren en het geheugen (Dannlowski et al, 2012; McEwen, 2010; Teicher et al., 2003, 2018; Whittle et al., 2016). Meegemaakte kindermishandeling is herhaaldelijk geassocieerd met een kleiner hippocampaal volume in mishandelde mensen met (Thomaes et al., 2010) en zonder psychopathologie (e.g., Dannlowski et al., 2012; Riem, Alink, Out, Van IJzendoorn, & Bakermans-Kranenburg, 2015). De hippocampus lijkt tevens betrokken te zijn bij opvoedingsgedrag (Swain, Lorberbaum, Kose, & Strathearn, 2007). Het is echter onbekend of hippocampaal volume ook verband houdt met mishandelend opvoedingsgedrag.

In **Hoofdstuk 3** van dit proefschrift hebben we onderzocht in hoeverre bilateraal hippocampaal volume samenhangt met zowel ervaren kindermishandeling als met mishandelend opvoedingsgedrag, waardoor we de potentiële rol van hippocampaal volume in IOKM hebben kunnen onderzoeken. Hierbij hebben we onderscheid gemaakt tussen (meegemaakte en gepleegde) mishandeling en verwaarlozing, aangezien verschillende vormen van mishandeling mogelijk differentieel geassocieerd zijn met hippocampaal volume (e.g., Hanson et al., 2015; Teicher & Samson, 2016). Eerder onderzoek laat zien dat sekse mogelijk ook een belangrijke factor is aangezien de hippocampus bij mannen gevoeliger lijkt te zijn voor stress dan bij vrouwen (e.g., Teicher & Samson, 2016; Whittle et al., 2016), hoewel associaties tussen PTSS en hippocampaal volume lijken te worden gedreven door vrouwen (Logue et al., 2018). Daarom hebben we in onze studie ook bekeken of sekse een rol speelt in de associatie tussen hippocampaal volume en meegemaakte mishandeling.

Samengevat lieten onze bevindingen in **Hoofdstuk 3** zien dat meegemaakte mishandeling voor mannen significant samenhing met een kleiner hippocampaal volume.

Dit resultaat kwam het duidelijkst naar voren bij de rechter hippocampus. Voor vrouwen hebben we echter geen significant verband gevonden tussen meegemaakte mishandeling en het volume van de hippocampus. Meegemaakte verwaarlozing hing bovendien in beide groepen niet significant samen met hippocampaal volume. Tot slot hebben we geen associaties gevonden tussen hippocampaal volume en mishandelend of verwaarlozend gedrag. Dit betekent dat we geen indicaties hebben gevonden voor een mediërende rol van het volume van de hippocampus in intergenerationele overdracht van mishandeling of verwaarlozing.

IOKM en de verwerking van dreiging in het brein

Naast het bestuderen van de mogelijk rol van de structuur van het brein in IOKM in **Hoofdstuk 3** hebben we ook onderzoek gedaan naar de rol van de functie van het brein. In **Hoofdstuk 4 en 5** van dit proefschrift hebben we ons gericht op het onderzoeken van de neurale correlaten van de verwerking van dreiging, in de vorm van twee belangrijke processen in de context van kindermishandeling, namelijk de verwerking van (negatieve) emotionele gezichten en sociale exclusie. Verstoringen van deze neurale processen zouden mishandelde ouders kwetsbaarder kunnen maken voor mishandeling van hun eigen kinderen en daarmee een rol kunnen spelen bij IOKM.

IOKM en de verwerking van emotionele gezichten in het brein

Het meemaken van kindermishandeling hangt samen met het ervaren van problemen op het gebied van emotionele reactiviteit en verwerking (e.g., Briere, 2002; Pozzi et al., 2020), wat zich onder andere uit in een overgevoeligheid voor (negatieve) emotionele gezichtsuitdrukkingen (e.g., Assed et al., 2020; Pollak & Tolley-Schell, 2003). Vanuit evolutionair perspectief is het nuttig om gezichtsuitdrukkingen snel te verwerken wanneer je als kind opgroeit in een thuissituatie waar sprake is van fysieke of emotionele dreiging, omdat daarmee signalen van zowel dreiging als veiligheid kunnen worden opgevangen. In de loop van de tijd kan een verhoogde reactiviteit op negatieve emotionele gezichten echter zorgen voor een verhoogd risico op het ontwikkelen van een aanhoudende waakzaamheid voor dreigingsgerelateerde gezichtsuitdrukkingen en een aandachtsbias voor bedreigende of negatieve informatie in het algemeen. Dit wordt geassocieerd met de ontwikkeling van psychopathologie (e.g., Gibb, Schofield, & Coles, 2009) en problemen met interpersoonlijke relaties (Cicchetti, Toth, & Maughan, 2000). Moeilijkheden met het verwerken van emotionele gezichten worden tevens in verband gebracht met insensitief ouderschap (e.g., Thompson-Booth et al., 2014). Dit maakt dat één van de mogelijke consequenties van meegemaakte kindermishandeling (namelijk veranderingen in de verwerking van emotionele gezichten) een potentiële risicofactor vormt voor mishandelend gedrag, waardoor het een mogelijk mechanisme zou kunnen zijn in IOKM (e.g., Asla, de Paúl, & Pérez-Albéniz, 2011; Wagner et al., 2015).

Emotieregulatieproblemen bij mensen die mishandeld zijn als kind lijken weerspiegeld te worden in chronische veranderingen in de neurale processen van het brein (Hart & Rubia, 2012; Hein & Monk, 2017). Zo laten volwassenen die in de kindertijd (emotioneel) mishandeld zijn bijvoorbeeld verhoogde bilaterale amygdala activiteit zien tijdens het bekijken van neutrale en emotionele gezichten (Dannlowski et al., 2012; McCrory et al., 2011b; Van Harmelen et al., 2013). De amygdala speelt een centrale rol in het verwerken van emotionele gezichten (e.g., Davis & Whalen, 2001). Veranderingen in de neurale verwerking van emotionele gezichtsstimuli in mishandelde mensen zijn echter ook gerapporteerd in andere hersengebieden, zoals de hippocampus, insula en inferieure frontale gyrus (IFG; e.g., Hart et al., 2018; Maheu et al., 2010; McCrory et al., 2011b). Hoewel deze hersengebieden (amygdala, hippocampus, insula en IFG) ook betrokken lijken bij opvoedingsgedrag (DeGregorio, 2013; Rilling & Mascaro, 2017; Swain & Ho, 2017), is nog onduidelijk of de impact van meegemaakte kindermishandeling op neurale responsiviteit tijdens het zien van emotionele gezichten in deze hersengebieden ook samenhangt met opvoedingsgedrag (waaronder mishandelend gedrag) in de volwassenheid.

Onderzoek naar de neurale correlaten van opvoedingsgedrag in het algemeen, en mishandelend gedrag in het bijzonder, is zeldzaam (León et al., 2019; Pozzi et al., 2020; Van IJzendoorn et al., 2020). De 3G Ouderschapsstudie is de eerste studie die onderzocht heeft of veranderingen in neurale reactiviteit tijdens het bekijken van emotionele gezichten (**Hoofdstuk 4**; en tijdens sociale exclusie in **Hoofdstuk 5**) een rol spelen bij IOKM. We hebben onderzocht of activatie in de amygdala, hippocampus, IFG en insula tijdens het zien van boze, bange, vrolijke en neutrale gezichten samenhangt met meegemaakte kindermishandeling en met mishandelend gedrag. Dit hebben we onderzocht in het fMRI sample van de 3G Ouderschapsstudie bestaande uit 171 participanten van 51 families (twee generaties) met een brede leeftijdsrange (8-69 jaar). Omdat verschillende typen mishandeling (mishandeling en verwaarlozing) differentiële effecten zouden kunnen hebben op de verwerking van dreiging en emotie (e.g., Compier-de Block, 2017) hebben we in onze studie onderscheid gemaakt tussen de effecten van (meegemaakte en gepleegde) mishandeling en verwaarlozing. Tot slot hebben we onderzocht of leeftijd de associatie tussen neurale reactiviteit op emotionele en neutrale gezichten en meegemaakte mishandeling en mishandelend gedrag modereert.

Onze resultaten wijzen op een associatie tussen neurale activatie in de amygdala en IFG en meegemaakte mishandeling, maar dit verband is niet gevonden voor mishandelend gedrag. We hebben een verhoogde bilaterale amygdala reactiviteit gevonden in reactie op angstige gezichten bij oudere mensen met een geschiedenis van verwaarlozing, terwijl we juist een verlaagde amygdala activatie hebben gevonden in reactie op hetzelfde type gezichten bij jongere mensen die verwaarlozing hebben meegemaakt. Dit zou erop kunnen duiden dat jongeren, die nog thuiswonen bij hun (mogelijk verwaarlozende) ouders, een vorm van terugtrekking vertonen of zelfs emotionele vermijding laten zien

van emotionele, of in onze studie voornamelijk angstige, gezichten. Bovendien hebben we gevonden dat meegemaakte mishandeling samenhangt met een verlaagde IFG activatie tijdens het bekijken van bange, vrolijke en neutrale gezichten bij jongere mensen, terwijl meegemaakte verwaarlozing juist samenhing met verhoogde IFG activatie tijdens het zien van dezelfde gezichten in dezelfde leeftijdscategorie. Bij oudere participanten verdwijnen deze tegengestelde effecten voor mishandeling en verwaarlozing. Onze resultaten wijzen dan ook op potentieel differentiële neurale effecten van meegemaakte mishandeling en verwaarlozing en op significante leeftijdseffecten. Onze bevindingen zouden erop kunnen wijzen dat verwaarloosde kinderen harder moeten werken om emotionele gezichten te verwerken, aangezien verwaarlozende ouders hun kinderen minder kansen bieden om emotionele signalen te leren interpreteren. Mishandelde kinderen hebben daarentegen meer interactie met hun ouders, maar worden daarbij vaker blootgesteld aan gedrag dat angst en overmatige waakzaamheid kan opwekken. Dit zou onze tegenovergestelde bevindingen met betrekking tot meegemaakte mishandeling en verwaarlozing kunnen verklaren (Bousha & Twentyman, 1984; Crittenden, 1981; Pollak, Cicchetti, Hornung, & Reed, 2000).

Mishandelend en verwaarlozend gedrag was tot slot niet geassocieerd met neurale reactiviteit in de amygdala, hippocampus, IFG of insula tijdens het bekijken van emotionele en neutrale gezichten. We hebben dan ook geen indicatie gevonden voor een rol van neurale responsiviteit bij het verwerken van emotionele gezichtsuitdrukkingen in IOKM.

IOKM en de reactie van het brein op sociale exclusie

Afwijzing door ouders vormt een belangrijk onderdeel van kindermishandeling (Bolger & Patterson, 2001; Glaser, 2002), namelijk in de vorm van agressie en vijandigheid ofwel via verwaarlozing en onverschilligheid (Loue, 2005). Chronische blootstelling aan afwijzing tijdens de kindertijd wordt in verband gebracht met emotionele, cognitieve, gedragsmatige en sociale problemen, hetgeen zich onder andere kan uiten in een laag zelfbeeld en overgevoeligheid voor signalen van dreiging en afwijzing (DeWall & Bushman, 2011; Eisenberger, 2012; Sreekrishnan et al., 2014; Van Beest & Williams, 2006). Afgewezen worden door eigen ouders kan zich vertalen in een meer algemene gevoeligheid voor sociale afwijzing in allerlei situaties, inclusief ouder-kind interacties in de volgende generatie.

Onderzoek laat zien dat er een netwerk van hersengebieden betrokken is bij het verwerken van sociale afwijzing en exclusie, waar de insula, anterieure cingulate cortex (ACC) en de mediale prefrontale cortex (mPFC) onderdeel van uitmaken (e.g., Bolling et al., 2011; Cacioppo et al., 2013; DeWall et al., 2010; Eisenberger, 2015; Eisenberger, Lieberman, & Williams, 2003; Rotge et al., 2015; Sebastian et al., 2011). Eerder onderzoek laat tevens een verandering in neurale reactiviteit zien tijdens sociale afwijzing bij mishandelde mensen, zoals een verhoogde dorsale mPFC activatie tijdens sociale exclusie bij jongvolwassenen die emotionele mishandeling hebben meegemaakt (Van Harmelen et al., 2014). Boven-

dien lijkt een geschiedenis van mishandeling invloed te hebben op neurale netwerken (inclusief de insula, ACC en mPFC) die ook betrokken lijken te zijn bij het reguleren van opvoedingsgedrag (Swain & Ho, 2017). Neurale processen in deze gebieden zouden daarom betrokken kunnen zijn bij IOKM. In het fMRI sample van de 3G Ouderschapsstudie (*n* = 144; 90 ouders en 54 kinderen) hebben wij deze hypothese onderzocht door de impact van meegemaakte en gepleegde mishandeling op de reactiviteit in de insula, dACC en dmPFC tijdens sociale exclusie te onderzoeken. In deze studie hebben we wederom onderscheid gemaakt tussen (meegemaakte en gepleegde) mishandeling en verwaarlozing, aangezien mishandeling en verwaarlozing differentieel gerelateerd zouden kunnen zijn aan de emotionele en neurale correlaten van sociale afwijzing (e.g., Compier-de Block et al., 2016; Nemeroff, 2016).

Aangezien kindermishandeling veelal binnen de familiaire context plaatsvindt en individuele verschillen in reactie op sociale exclusie afhankelijk kunnen zijn van de relatie met de persoon die buitensluit (Bernstein, Sacco, Young, Hugenberg, & Cook, 2010; Krill & Platek, 2009; Sacco, Bernstein, Young, & Hugenberg, 2014; Scanlon, 2015) is een belangrijke vraag of mishandelde mensen een algemene gevoeligheid voor afwijzing ontwikkelen of een meer specifieke hypervigilantie voor afwijzing binnen de familiaire context. Om deze vraag te beantwoorden hebben we in **Hoofdstuk 5** de neurale responsiviteit tijdens exclusie door iemands eigen moeder of kind versus onbekenden onderzocht en hoe dit specifiek wordt beïnvloed bij mishandelde en mishandelende mensen.

Exclusie door onbekenden bleek voornamelijk geassocieerd met verhoogde activatie in de linker insula, terwijl exclusie door een familielid voornamelijk samenhing met verhoogde activatie in de ACC. Meegemaakte mishandeling, maar niet mishandelend gedrag, was geassocieerd met neurale reactiviteit tijdens sociale exclusie door onbekenden in de insula, ACC en dmPFC. Mishandelde ouders en kinderen lieten hogere activatie in de linker en rechter insula en dmPFC zien en lagere activatie in de dACC tijdens sociale exclusie door onbekenden. Hogere linker insula en dmPFC activatie tijdens sociale exclusie door onbekenden hing voornamelijk samen met meegemaakte verwaarlozing. Tegen onze verwachtingen in was meegemaakte mishandeling of verwaarlozing niet gerelateerd aan een verandering in activatie in de insula, dACC of dmPFC tijdens exclusie door een familielid. Het is mogelijk dat we met de specifieke selectie van hersengebieden andere belangrijke gebieden gemist hebben. Een tweede mogelijke verklaring voor onze bevindingen is dat mishandelde mensen relatief ongevoelig zijn geworden voor afwijzing door hun eigen familie, terwijl ze juist gevoeliger zijn geworden voor afwijzing in andere situaties (en dus door onbekenden).

Met behulp van exploratieve analyses vonden we tevens associaties tussen mishandelend gedrag van ouders met neurale reactiviteit tijdens exclusie in andere hersengebieden, namelijk de pre- en postcentrale gyrus. Lagere activatie in deze gebieden zou erop kunnen wijzen dat mishandelende ouders minder gevoelig zijn voor negatieve emotionele

en sociale prikkels en minder empathisch zijn. Onze resultaten wijzen op verschillende neurale correlaten van meegemaakte en gepleegde mishandeling. We hebben in deze studie dan ook geen mechanismen gevonden die betrokken zijn bij IOKM. Overgevoeligheid voor sociale afwijzing door vreemden bij verwaarloosde mensen onderstreept het belang van onderscheid maken tussen effecten van mishandeling en verwaarlozing en suggereert dat de invloed van het ervaren van afwijzing en mishandeling door eigen ouders zich niet alleen beperkt tot de gezinscontext maar ook daarbuiten reikt. Hypergevoeligheid voor sociale afwijzing door onbekenden kan helpen verklaren waarom mishandelde (en voornamelijk verwaarloosde) mensen moeilijkheden ervaren met sociale relaties (DeGregorio, 2013).

Conclusie

In dit proefschrift hebben we de impact van verschillende typen stressvolle en traumatische gebeurtenissen onderzocht. Met behulp van een grootschalige multi-informante, multigenerationele familiestudie hebben we de rol van structurele en functionele neurale correlaten van de verwerking van dreiging in IOKM onderzocht. Onze bevindingen lieten zien dat hippocampaal volume en neurale reactiviteit tijdens sociale exclusie en het bekijken van emotionele gezichten geassocieerd zijn met meegemaakte kindermishandeling, maar niet met mishandelend gedrag. Hoewel exploratieve analyses lieten zien dat mishandelende ouders een lagere reactiviteit vertoonden in de precentrale en postcentrale gyrus tijdens afwijzing door onbekenden, hebben we in onze andere twee fMRI studies geen neurale correlaten van mishandelend of verwaarlozend opvoedingsgedrag gevonden. We hebben daarom geen neurale mechanismen kunnen identificeren die betrokken lijken te zijn bij IOKM. Meer onderzoek naar de rol van het brein in mishandelend opvoedingsgedrag is noodzakelijk, aangezien hier tot op heden nog nauwelijks iets over bekend is (Van IJzendoorn et al., 2020). Hoewel er nog een lange weg te gaan is, levert fMRI-onderzoek naar de impact van trauma een bijdrage aan de ontwikkeling van nieuwe interventies, waaronder hersenstimulatie, neurofeedback en cognitief-emotionele training (Norbury, Perez-Rodriguez, & Feder, 2019). Sommige van deze interventies worden in de praktijk reeds geïmplementeerd (Greenberg, 2006; Keynan et al., 2019; Waugh & Koster, 2015).

De resultaten van dit proefschrift benadrukken tevens het belang van het maken van onderscheid tussen de verschillende subtypen van kindermishandeling (mishandeling en verwaarlozing) in wetenschappelijk onderzoek en in de klinische praktijk en wijzen erop dat de impact van het ervaren van afwijzing en mishandeling door eigen ouders tot buiten de familiare context reikt. Het is verder van essentieel belang om bewustwording te verhogen van de schadelijke gevolgen van stressvolle levensgebeurtenissen die niet als traumatisch worden geclassificeerd volgens het DSM A1 criterium, en verwaarlozing in het bijzonder, aangezien de uitkomsten minstens zo ernstig kunnen zijn als de uitkomsten van traumatische A1 gebeurtenissen zoals kindermishandeling. We adviseren clinici daarom

om meer aandacht te besteden aan PTSS-symptoomprofielen in plaats van de strikte definitie van het A1 criterium van PTSS aan te houden. Bovendien mag de rol van sekse in de impact van trauma niet worden onderschat. Meer onderzoek naar de impact van trauma en mechanismen die mogelijk een rol spelen bij IOKM is van groot belang om de schadelijke effecten van trauma te verminderen en kindermishandeling te voorkomen. Het overbruggen van de kloof tussen wetenschap en klinische praktijk is essentieel om de cyclus van kindermishandeling te doorbreken en de impact van trauma te verminderen.

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Compier-de Block, L.H.C.G., Linting, M., **Van den Berg, L.J.M.**, Voorthuis, A., Tollenaar, M.S., Pittner, K., Buisman, R.S.M., Elzinga, B.M., Bakermans-Kranenburg, M.J., & Alink, L.R.A. The role of maltreatment history and emotion recognition in parent-to-child maltreatment. *Manuscript in preperation.*

CURRICULUM VITAE

Lisa Joy Margareth van den Berg werd geboren op 22 oktober 1986 in Rotterdam. Na het afronden van het Gymnasium in 2005 startte zij haar studie Psychologie aan de Erasmus Universiteit Rotterdam (EUR). In 2007 studeerde ze een half jaar aan de University of the Fraser Valley in Canada. In 2010 behaalde ze haar Masterdiploma Klinische Psychologie aan de EUR. Tijdens haar Master deed zij klinische ervaring op tijdens een stage op de afdeling Angststoornissen van PsyQ Rijnmond en schreef ze haar scriptie over angst en fantasie bij jonge kinderen. Tevens werkte ze in 2010 als onderzoeksassistent mee aan verschillende onderzoeksprojecten van de Vrije Universiteit Amsterdam en de EUR, onder andere naar de neurale effecten van rook- en cocaïneverslaving. Aansluitend op haar Master volgde Lisa van 2010 tot 2011 het Advanced Research Program aan de EUR. Tijdens deze Research Master werkte zij mee aan het opzetten van verschillende projecten, waaronder een studie naar de effectiviteit van een werkgeheugentraining voor angstige en depressieve patiënten en een onderzoek naar de impact van repressieve coping op gezonde kinderen en kinderen met kanker. Van 2009 tot 2011 werkte ze tevens als tutor en trainer aan de EUR waar zij voor diverse vakken onderwijsgroepen begeleidde voor studenten Psychologie en waar zij Masterstudenten heeft begeleid bij het schrijven van hun scriptie.

In 2011 werd Lisa aangesteld als promovenda aan de afdeling Klinische Psychologie van de Universiteit Leiden en onderzocht de impact van verschillende typen traumatische en stressvolle levensgebeurtenissen, met een focus op de rol van het brein in de intergenerationele overdracht van kindermishandeling en verwaarlozing. De resultaten van haar onderzoek zijn beschreven in dit proefschrift. Tijdens haar promotietraject verrichtte Lisa tevens diverse onderwijstaken, waaronder het begeleiden van studenten in het kader van hun afstudeerscriptie en het begeleiden van diverse onderwijswerkgroepen voor Bachelor- en Masterstudenten Psychologie. Ze heeft bovendien diverse presentaties verzorgd op nationale en internationale congressen en in 2014 een reisbeurs ontvangen van het Leiden University Fund (LUF) voor het presenteren van haar onderzoek op het jaarlijkse congres van de International Society for Traumatic Stress Studies (ISTSS) in Miami. In 2017 is Lisa gestart met de postdoctorale opleiding tot GZ-Psycholoog bij Yulius (specialistische GGZ instelling, locatie Barendrecht) op de afdelingen Gezinspsychiatrie, FACT Jeugd en Gezin en de Polikliniek ASS Kind en Jeugd. In 2020 heeft zij deze opleiding succesvol afgerond. Momenteel is ze werkzaam als GZ-Psycholoog en regiebehandelaar op de Polikliniek ASS Kind en Jeugd en deeltijdbehandeling ASS Orion van Yulius. Lisa woont in Barendrecht samen met haar man Alexander Verhaar en hun 2-jarige zoon Samuel.

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