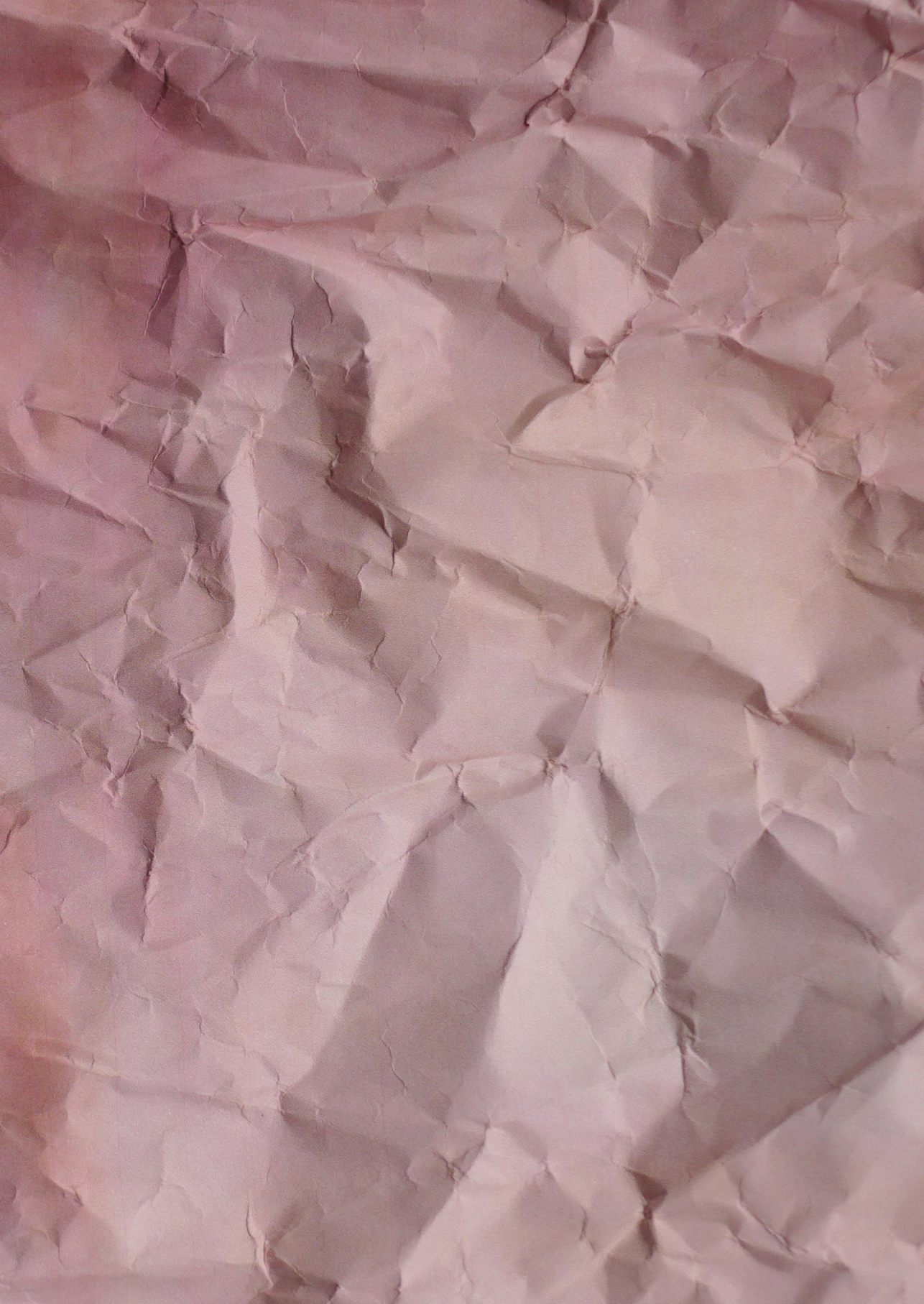
The impact of trauma: a focus on the neural correlates of intergenerational transmission of child maltreatment

Berg, L.J.M. van den



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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