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.

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). It was striking that whereas in the A1 event group women showed significantly higher PTSD symptoms than men, in the non-A1 event group there were no gender differences in PTSD symptoms. 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. 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 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.

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). 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). 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.

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.

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 neural alterations (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 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. 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 neglect was associated with higher IFG activation in this age group while viewing these faces. These effects disappeared with increasing age.

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 sample of the 3G Parenting study (*n* = 144). 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. 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. 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).

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.

This dissertation 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.

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. 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.