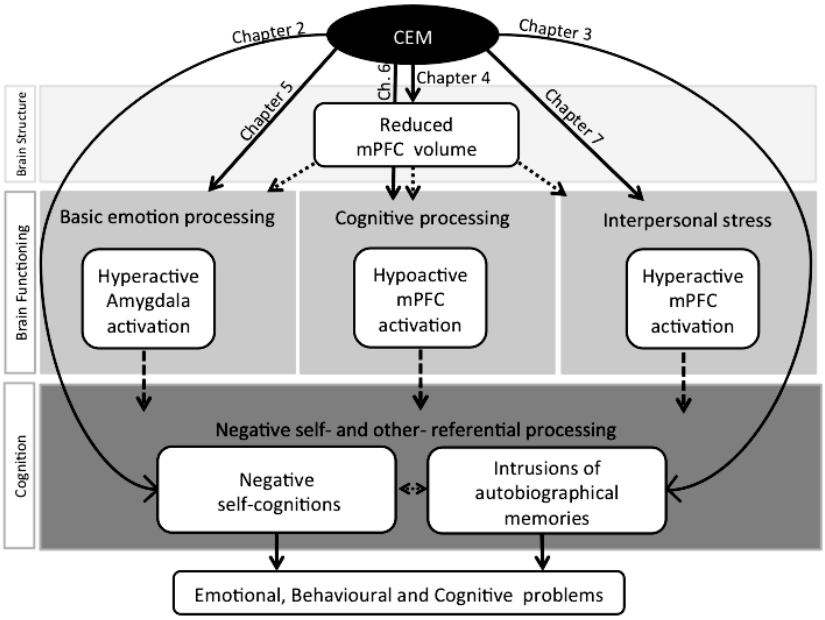
Chapter 8: Summary and Discussion

The impact of Childhood Emotional Maltreatment (CEM) on cognition and the brain

The primary objective of this thesis was to investigate the long-term impact of CEM on cognition and the brain (structure and functioning). Figure 1 provides an overview of the findings in this thesis.

Figure 1. Schematic overview of the findings in this thesis.



Note. The arrows display the direct impact of CEM on cognition and the brain as measured in this thesis. These arrows indicate the impact of CEM on cognition (chapters 2 and 3) and the brain (chapters 4,5,6,7). Dashed arrows display hypothesized impacts that are suggested by the findings of this thesis, but not explicitly examined. Ch. = chapter.

THE IMPACT OF CEM ON COGNITION

In Chapter 2 we examined CEM related negative self-cognitions. To this end, we investigated automatic (and explicit) self-depression and/or self-anxiety associations in the Netherlands Study of Depression and Anxiety (NESDA) sample (N = 2981). Automatic self- associations were assessed using the Implicit Association Test. We found that CEM was related to enhanced automatic and explicit self-depression and self-anxiety associations. In addition, these automatic and explicit negative self-associations both partially mediated the association between CEM and depressive or anxious symptomatology.

Implicit negative self-associations are of importance because they are predictive of immediate affective behavior (Engelhard, Huijding, Van den Hout, & De Jong, 2007; Haeffel et al., 2007), and are therefore suggested to play a pivotal role in the maintenance of psychopathology. Increased negative self-associations are hypothesized to enhance (negative) bias and recall when engaged in new situations, and when retrieving memories (Beck, 2008), which may result in more frequent and more intense negative experiences, which in turn may enhance negative self-associations. Due to this process, emotionally abused individuals may be more vulnerable to develop and/or maintain a depressive and/or anxiety disorder (Beck, 2008).

We investigated CEM related negative and positive autobiographical memory processing in Chapter 3. We found that, when trying to cope with negative interpersonal experiences, individuals reporting severe CEM employed more cognitive avoidant strategies in order to suppress thinking about these negative memories. We also investigated the impact of CEM on the experience of positive and negative autobiographical memory intrusions, using a thought suppression task. We examined intrusions during and immediately after active suppression in a sample of healthy young adults reporting Low, Moderate and Severe CEM, or No Abuse (total N=83). During active suppression, we found no CEM related differences in the amount of intrusions for both negative and positive autobiographical memories. However, immediately after active suppression, individuals reporting severe CEM reported *more* intrusions of both positive and negative autobiographical memories than the other three groups. Importantly, the number of negative memory intrusions was positively related to general psychiatric distress.

Thus, individuals reporting CEM were quite effective when actively trying to divert their thoughts. Yet, when no longer instructed to suppress thinking about their autobiographical memories, the intrusions did not subside in these individuals, whereas the number of post-suppressive intrusions did decrease in individuals reporting no to moderate CEM. It is of note that individuals reporting severe CEM indicated that they experienced similar amounts of both *negative* and *positive* autobiographical memory intrusions. This may suggest that they are not as adept at cognitive avoidance strategies on a long term. Another explanation may be that individuals reporting

severe CEM keep processing (i.e. suppressing) interpersonal memories due to the enhanced (positive and negative) emotionality of those memories. This would suggest a general sensitivity towards both negative and positive autobiographical memories.

Taken together, this thesis provides evidence that CEM is related to more *negative* self-referential thinking (negative self-cognitions), and more *frequent* self and other-referential thinking (intrusions of negative and positive interpersonal autobiographical memories) (see Figure 1). In line with the idea that negative self-cognitions enhance emotional and cognitive vulnerability (Beck, 2008), self-cognitions mediated the relationship of CEM with depressive and anxious symptoms (Chapter 2), and negative memory intrusions were positively related to general distress (Chapter 3). These findings may be important in explaining the behavioral, emotional and cognitive problems reported in individuals with CEM (see introduction of this thesis).

The impact of CEM on brain structure

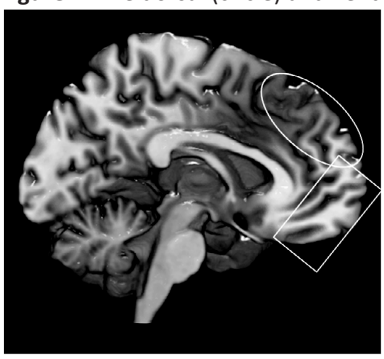
The impact of CEM on brain structure was examined in chapter 4. Using high-resolution T1-weighted 3T MRI anatomical scans and a whole-brain optimized Voxel Based Morphometry approach, we examined whether healthy controls and unmedicated patients with depressive and/or anxiety disorders reporting CEM (n=84) displayed structural brain changes compared to controls and patients who reported no childhood abuse (n=97). We found that self-reported CEM was associated with a significant reduction in predominantly left dorsal medial prefrontal cortex (mPFC) volume, even in the absence of physical and/or sexual abuse during childhood (Figure 1). In addition, reduced mPFC in individuals reporting CEM was present in males and females, and was independent of concomitant psychopathology.

Our findings of CEM related reductions in mPFC volume echo those of numerous animal studies utilizing paradigms that closely resemble CEM, such as maternal separation or isolation rearing (Czéh et al., 2007; Goldwater et al., 2009; Liston et al., 2006; Sánchez, Ladd, & Plotsky, 2001; Sanchez et al., 2007). Moreover, our findings have also been replicated in human subjects (Ansell, Rando, Tuit, Guarnaccia, & Sinha, 2012; Dannlowski, Stuhrmann, et al., 2012; Edmiston et al., 2011; Tomoda et al., 2011). Taken together, both animal and human studies corroborate our findings that a history of CEM leads to a volumetrically smaller dorsal mPFC that can be found even 25 years after the emotional abuse took place.

The medial prefrontal cortex

The mPFC is anatomically located in the medial wall of the frontal lobe, superior to the anterior cingulate cortex. The mPFC can be roughly divided into two subsections, the dorsal and the ventral mPFC (see Figure 2) (Etkin, Egner, & Kalisch, 2011; Phillips, Drevets, Rauch, & Lane, 2003). Both the dorsal and the ventral mPFC have extensive connectivity with the amygdala and hippocampus.

Figure 2. The dorsal (circle) and ventral (square) mPFC.



The mPFC is crucial for emotional behavior, emotion regulation, and for regulation of the stress response (Cardinal, Parkinson, Hall, & Everitt, 2002; Etkin et al., 2011; Phillips et al., 2003). For instance, the mPFC is involved in the regulating, recalling, generating, expression and conscious appraisal of fear, anxiety, emotional conflict (Etkin et al., 2011; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). Within the mPFC, the *dorsal* mPFC seems to function as the main hub for the processing, appraisal and expression of negative emotions (i.e. fear, anxiety, emotional conflict) (Etkin et al., 2011), whereas, activation in the *ventral* mPFC has been linked with regulatory responses to both negative and positive emotions (Etkin et al., 2011). It has been suggested that the ventral mPFC regulates emotional responses through its inhibition of amygdala activity; a key brain region for automatic (bottom-up) emotion processing, salience detection, and fear conditioning (Anderson, 2007; Davidson, 2002; Hermans et al., 2011; Kim et al., 2011; Lindquist et al., 2012; Pessoa & Adolphs, 2010; van Marle, Hermans, Qin, & Fernández, 2009; Whalen, 2007).

The dorsal and ventral mPFC are functionally intertwined (Etkin et al., 2011; Phillips et al., 2003; Radley et al., 2004). Indeed, during top-down emotion regulation, it appears that the dorsal mPFC modulates fear response through its regulatory role on the ventral mPFC, which in turn dampens amygdala activity (Etkin et al., 2011, also Kim et al., 2011; Milad et al., 2009). Besides emotion appraisal and regulation, the mPFC plays a crucial role in self-referential processing (Blair et al., 2012; Grimm et al., 2009; Lemogne et al., 2009; Lindquist et al., 2012; Moran, Macrae, Heatherton, Wyland, & Kelley, 2006; van der Meer, Costafreda, Aleman, & David, 2010; Yoshimura et al., 2009). Indeed, greater mPFC activity is related to *more* self-referential processing in depressed patients (Lemogne et al., 2009), and in patients with generalized anxiety disorder (Blair et al., 2012).

During self-referential processing, there also appear to be distinct functional associations for the *dorsal* and *ventral* mPFC. For instance, the

ventral mPFC has been associated with *self*-referential processing, whereas the dorsal mPFC has been implicated in *other*-referential processing (Amodio & Frith, 2006; Mitchell, Macrae, & Banaji, 2006). Furthermore, a recent model for self-reflective processing in the brain implicated a pivotal role for the dorsal, and ventral mPFC, as well as the posterior ACC (Van der Meer et al., 2010). In this model, the dorsal mPFC is critical in the evaluation and decision-making processes of self-and other referential information (the evaluation whether information is relevant to the self). The ventral mPFC plays a key role in the more *affective* component of self-reflective processing, through emotional appraisal of self-relevant information and the coupling of emotional and cognitive processing during self-referential processing. Finally, in this model, the posterior ACC is involved in the integration of autobiographical memory with emotional information about the self.

Taken together, there are clear indications that the mPFC is pivotal in regulating emotional behavior, stress response and self-referential processing. Therefore, our findings of reduced mPFC volume may be related to altered functioning of this region, or in connected regions such as the amygdala, during emotional brain functioning.

THE IMPACT OF CEM ON EMOTIONAL BRAIN FUNCTIONING

INCREASED LIMBIC ACTIVATION DURING BASIC EMOTION PROCESSING

In Chapter 5 we examined the neurobiological impact of CEM during emotion processing. To this end, we examined amydala and mPFC reactivity to faces (*Angry, Fearful, Sad, Happy, Neutral*) versus scrambled faces in healthy controls and unmedicated patients with depressive and/or anxiety disorders reporting CEM before the age of 16 (n=60). We compared these individuals with controls and patients who did not report childhood abuse (n=75). In this study, we found that CEM was associated with enhanced bilateral amygdala reactivity to emotional facial expressions in general, independent of psychiatric status, severity of depressive or anxious symptoms, neuroticism, parental psychiatric status, or gender.

Preclinical studies show that maternal separation has been associated with enhanced fear response in animals (Feng et al., 2011; Oomen et al., 2010). In line with these preclinical studies, a longitudinal study in soldiers showed that combat stress also increases amygdala responsivity to biologically salient stimuli. More importantly, rather than actual threat exposure, the *perceived* threat exposure appeared crucial in changing amygdala regulation (Van Wingen, Geuze, Vermetten, & Fernández, 2011). In line with the suggestion that psychological threat can alter amygdala functioning, a history of severe neglect has been associated with enhanced amygdala responsivity in adolescents (Maheu et al., 2010). Furthermore, an abundance of recent studies replicated the CEM related amygdala hyper-vigilance towards the detection of emotional faces (Dannlowski, Kugel, et al., 2012; Dannlowski, Stuhrmann, et al., 2012; McCrory et al., 2011, 2013). Taken together, our findings suggest that CEM is related to a lasting

enhancement of amygdala response towards the detection of negative and positive emotional facial expressions in others (Figure 1).

We found no support for differential mPFC functioning during emotional face processing in patients and controls reporting CEM. This suggests that amygdala hyper-responsivity to emotional facial perception in adults reporting CEM may be independent from top-down regulatory influences of the mPFC. This is in line with findings of normal mPFC–amygdala connectivity in individuals with CEM (Van der Werff et al., 2012). An alternative explanation may be that we used a gender-labeling task that requires minimal cognitive resources (Reddy et al., 2004). It might be that abnormal mPFC functioning related to CEM is only observed in tasks posing greater cognitive demands (see for example Shin et al., 2006).

Interestingly, hyperactivation of the amygdala in adults reporting CEM was not only found for negative, but was also present for positive facial expressions. This might indicate that individuals with a history of CEM misinterpret all facial expressions as threatening. Happy faces might be interpreted as a mask for more malevolent emotions (Pollak et al., 2000), for example as being laughed at. This would be in line with the finding that neglected children have poor valence discriminatory abilities for different emotional facial expressions (Pollak et al., 2000; Fries & Pollak, 2004; Vorria et al., 2006), suggesting that they may misinterpret all emotional faces as potentially threatening (Pollak et al., 2000). An alternative explanation may be that enhanced amygdala activation in response to happy faces is indicative of increased sensitivity towards *positive* emotional expressions in others, in the sense that happy faces might function as safety signal.

CEM RELATED MPFC HYPOACTIVITY DURING EMOTIONAL MEMORY

In Chapter 6, we investigated CEM-related differential activations in the mPFC during the encoding and recognition of positive, negative, and neutral words using fMRI. Our sample (*N*=194) consisted of patients with depression and/or anxiety disorders and Healthy Controls (HC) reporting CEM (n=96), and patients and HC reporting No Abuse (n=98). In this study, we found a consistent pattern of mPFC hypoactivation during the encoding and recognition of positive, negative, and neutral words in individuals reporting CEM (Figure 1). These findings were not explained by psychopathology, severity of depression or anxiety symptoms, nor were these findings explained by gender, level of neuroticism, parental psychopathology, negative life events, antidepressant use, or decreased mPFC volume in the CEM group.

Hypoactivation in the mPFC was found for negative and positive words in individuals reporting CEM. This is in line with our findings of CEM related autobiographical memory intrusions, and emotional face processing. However, on a behavioral level, we did not find similarly reduced cognitive processing; the CEM group was as accurate and fast in categorizing words as the No Abuse group. Hence, mPFC hypoactivation in individuals reporting

CEM may resemble a more general blunting of cognitive (cortical) processing in these individuals. Individuals reporting CEM may require less cognitive and related mPFC processing in order to correctly recognize emotional words later on.

Hypoactive mPFC responsivity in patients and controls reporting CEM may also be explained by changes in self-reflective processing, since the mPFC is crucial for self- and other referential thinking (Van der Meer et al., 2010). In line with this hypothesis we found that individuals reporting CEM reported enhanced negative self-associations (chapters 2) and more frequent self- and other-referential thinking (i.e. intrusions; chapter 3). Therefore, hypoactive mPFC activation in individuals reporting CEM may also indicate that these individuals attenuate their negative self- and/or other-referential thinking during emotional memory in order to focus on the task at hand.

CEM RELATED MPFC HYPER ACTIVITY TO INTERPERSONAL STRESS

In chapter 7 we examined the neural responses during interpersonal/social stress in young adult patients and controls reporting low to extreme CEM. Social stress response was induced using social exclusion in the Cyberball task during fMRI scanning (Williams & Jarvis, 2006). We investigated brain responses and self-reported distress to social exclusion in 46 young adults including patients reporting severe CEM (n=26), and healthy controls (n=20). On a behavioral level, we found that social exclusion was related to a decrease in mood and an increase in needs threat (i.e. reduced self-esteem, sense of belonging, meaningful existence, and control) in our sample. Furthermore, although individuals reporting severe CEM group did not report lower mood or higher needs threat than the control group after exclusion, they reported lower mood and higher needs threat at post measurement (after scanning). Therefore, our findings suggest that severe CEM is related to longer recovery periods after social exclusion in these individuals. On a neural level in the brain we found that social exclusion was related to increased activity in the subgenual ACC and posterior cingulate cortex across participants, which is consistent with prior social exclusion studies (Eisenberger, 2012). Furthermore, we found that, during social exclusion, the severity of CEM was positively associated with dorsal mPFC responsivity for all participants (Figure 1).

Dorsal mPFC responsivity related to the severity of a history of CEM may be explained by the fact that social exclusion enhances self- and other-reflective processing (i.e. social uncertainty, distress, and social rumination) (for an overview see Cacioppo et al., 2013). During social exclusion, we found increased activity in posterior ACC, and ventral mPFC in our sample. These regions have been implicated in a recent model for self-reflective processing (Van der Meer et al., 2010). Crucially, in this model, the dorsal mPFC is important for the evaluation and decision making of self-and other referential information (the evaluation whether information is relevant to the self). Therefore, hyperactivity in the dorsal mPFC during social stress in

individuals reporting CEM may be explained by increased negative self- and other-referential processing in these individuals. This is in line with our findings in chapter 2 and 3 where we showed that individuals reporting CEM show enhanced negative self-cognitions (chapter 2), and more frequent negative self-referential processing (chapter 3) on a cognitive level.

DYSFUNCTIONAL REAPPRAISAL?

In this thesis, it is important to note that we did not find evidence for a specific sensitivity towards negative material alone. We found that individuals reporting CEM showed similar brain functioning for positive and negative material, both on a neuronal level when processing happy emotional faces and positive emotional words, and on a cognitive level when trying to suppress positive interpersonal memories. These findings may be explained by dysfunctional re-appraisal of positive stimuli. However, for the thought suppression task in Chapter 3, individuals reporting CEM used autobiographical memories that they themselves considered to be very positive. Therefore, equal amounts of intrusions of positive and negative memories cannot be explained by dysfunctional re-appraisal of those positive memories. Rather, these findings are more in line with the suggestion of equally enhanced sensitivity for negative and positive stimuli in individuals reporting CEM. In order to tailor therapeutic interventions for these individuals, it is important to further investigate this sensitivity towards positive material in individuals reporting CEM.

CEM AND OTHER TYPES OF ABUSE

We found enhanced negative self-cognitions in individuals reporting only CEM, and in individuals reporting CEM and concurrent physical and sexual abuse. Furthermore, CEM related reduction in mPFC volume, enhanced amygdala functioning, and hypo and hyperactive mPFC functioning were found independent of concurrent physical and sexual abuse. These findings are in line with the suggestion that CEM is the core feature of a negative family environment in which other types of abuse may co-occur. Furthermore, these findings suggest that the impact of CEM on cognition and the brain is at least as severe as the impact of physical and sexual abuse.

A NEUROCOGNITIVE MODEL FOR EMOTION DYSFUNCTION AFTER CEM

To summarize, on a neuroanatomical level we showed that CEM is related to dorsal mPFC reductions that can be observed in adulthood (chapter 4, Figure 1). The mPFC plays a crucial role in emotional behavior, emotion regulation, self- and other- referential thinking, and stress response (Etkin et al., 2011; Phillips et al., 2003; Radley et al., 2004). Therefore, a smaller mPFC may be related to altered emotional functioning in this region (Buchanan et al., 2010; Goldwater et al., 2009; Schubert, Porkess, Dashdorj, Fone, & Auer, 2009). Indeed, in children with early life stress reductions in the PFC have been linked with poor cognitive performance (which is assumed to be

dependent on PFC functioning) (Hanson et al., 2012). These results suggest that reduced volume in a brain region may lead to altered functioning within that region.

We found that CEM indeed impacts brain functioning in the mPFC and in the amygdala, a region that has substantive connectivity with the mPFC. During more basic/automatic brain functioning, we found that individuals reporting CEM show amygdala hyper-responsivity to emotional faces. These findings suggest that individuals reporting CEM have persistent vigilance towards the detection of (negative and positive) emotional facial expressions in others (chapter 5). In addition, during tasks that are associated with more cognitive processing, we found CEM related altered functioning in the mPFC. Specifically, hypoactive mPFC activity was found during emotional memory processing (chapter 6), whereas hyperactivity in the mPFC was found in response to interpersonal stress (chapter 7). These findings suggest altered mPFC activity in individuals reporting CEM, and may be dependent on attenuation (hypoactivity), or an increase (hyperactivity) in negative self- and other-referential processing. In line with the suggestion of altered self-processing in CEM, CEM has been reported to have a negative impact on resting state functional connectivity in self-processing networks in the brain (Van der Werff et al., 2012).

Increased negative self-associations, in itself, are hypothesized to enhance (negative) bias and recall when engaged in new situations, and when retrieving memories, resulting in more frequent and more intense negative experiences, which in turn may enhance negative self-associations, etc. Indeed, on a cognitive level, we found that CEM is related to more *negative* self-referential thinking (negative self-cognitions; chapters 2), and more *frequent* self and other-referential thinking (intrusions of negative and positive interpersonal autobiographical memories; chapter 3). Finally, we found that self-cognitions mediated the association of CEM with depressive and anxious symptoms (chapter 2), and negative memory intrusions were strongly related to psychiatric distress (chapter 3). In line with this, negative self-cognitions have been found to be predictive of the course of depressive and anxiety disorders (Glashouwer, de Jong & Penninx, 2012).

To summarize, our findings suggest a model were CEM alters brain structure and brain functioning, which underlies maladaptive automatic and explicit (cognitive) negative self- and other- reflective processing (Figure 1). Individuals reporting CEM may be able to reduce this negative self- and other reflective processing during basic cognitive processing (i.e. memory processing). However, during more automatic emotion processing (i.e. emotional face processing) that occurs without cognitive processing and during interpersonal stress, this altered brain functioning may ultimately lead to an enhancement of negative self-referential processes, and stronger negative self-cognitions. Although this is a preliminary model awaiting futher empirical support, this model might explain why individuals reporting CEM show behavioural, emotional and cognitive problems in later life (see introduction of this thesis).

THE MECHANISMS THROUGH WHICH CEM LEADS TO PSYCHOPATHOLOGY

The second objective of this thesis was to examine whether CEM related alterations in cognition and the brain could explain how CEM leads to psychopathology in later life. In contrast to our expectations, the impact of CEM on cognition and the brain was not found to be more prominent in those individuals with a psychiatric diagnosis. Rather, the enhanced negative self-associations, reduction in mPFC, enhanced amygdala, and altered mPFC functioning was present in both patients and controls in chapters 2, 4, 5, 6 and 7. This indicates that CEM related maladaptive cognitions, reduced mPFC structure and altered brain functioning do not constitute 'a direct pathway' through which CEM necessarily leads to the development of depressive and/or anxiety disorders. Our findings more likely reflect vulnerabilities or risk factors that require an additional 'trigger' (such as a stressful life event) in order to lead to the development of depressive and/or anxiety disorders. In this section I will further elaborate on this in the light of the most prevailing models of trauma related psychopathology.

COGNITIVE AND NEUROBIOLOGICAL SCARS OF CEM?

The *'scar hypothesis of depression'* (Lewinsohn, Steinmetz, Larson, & Franklin, 1981; Wichers, Geschwind, van Os, & Peeters, 2009) is based on the idea that psychosocial stress can induce long-lasting neurobiological consequences ('scars'), rendering an individual more vulnerable to *subsequent* stress (Post, 1992). According to the scar hypothesis, depressive episodes leave scars that persist after remission and recovery. These scars increase individual's vulnerability to the onset of future depressive episodes when faced with additional psychosocial stress in later life. Scarring in this hypothesis refers to *persistent* changes that can occur on a wide range of domains; i.e. cognitive, emotional, and neurobiological (see Wichers et al., 2009). In accordance with the scar hypothesis of depression, our findings suggest that CEM is related to cognitive and neurobiological changes (*'scars'*) that persist into adulthood. These scars may constitute a vulnerability phenotype that increases sensitivity to the development of psychopathology when faced with stressors in later life. This is in line with our neurocognitive model and with the findings reported in chapter 4 where we found that *patients* reporting CEM reported more negative life events than *healthy controls* reporting CEM. Perhaps, the CEM induced phenotype (i.e. reduced mPFC volume in this case) interacted with stressful life events in adulthood to lead to a depressive or anxiety disorder in these individuals. In line with this, negative life events are predictive of the course of depressive and anxiety disorders (Spinhoven et al., 2011).

Interestingly, according to the scar hypothesis of depression, scars may wax and wane over time (Wichers et al., 2009). For instance, whereas additional stress enhances scarring, protective genotypes or therapy may

reduce scarring (Wichers et al., 2009). Therefore, the scar theory suggests that therapy may be a potential mechanism through which the cognitive and neurobiological scars of CEM may be reduced.

Stress-vulnerability and differential susceptibility models

Similar to the scar theory of depression, Gene-Environment (i.e. CEM) interactions may also explain why our findings of CEM related cognitive and neurobiological alterations do not necessarily lead to psychopathology. Such Gene×Environment interactions are described by the diathesis stress, or vulnerability/stress model (Monroe & Simons, 1991; Nuechterlein & Dawson, 1984). This model postulates that psychological disorders occur when a susceptible person meets with adverse/ stressful conditions. In line with the suggestion of Gene×CEM interactions, there are some indications that CEM related amygdala responsivity is modulated by mineralocorticoid receptor iso/val (rs5522) (Bogdan, Ph, Williamson, & Hariri, 2012), FK506 binding protein 5 (White et al., 2012), and neuropeptide Y genotype (Opmeer et al., 2013). It is important to note that besides genotype, susceptibility/ vulnerability factors in this model can also be behavioral (e.g. negative self-cognitions), and physiological (such as enhanced mPFC response).

A recent extension of the diathesis stress model; the differential susceptibility model (Belsky & Pluess, 2009; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2011) proposes that vulnerability to stress is neurobiological in nature. This neurobiological susceptibility underlies individuals' behavioral vulnerability (such as negative self-referential thinking), and interacts with genotype to modulate individuals' vulnerability. Therefore the differential susceptibility model suggests that CEM related reduced mPFC volume, altered mPFC responsivity, and enhanced amygdala response may increase vulnerability on a neuronal level. This increased neuronal sensitivity may underlie our findings of more negative self-referential cognitions (chapter 2), and more frequent self- and other referential processing on a cognitive level (chapters 3). This would be in line with our neurocognitive model of the impact of CEM (see Figure 1).

According to the differential susceptibility model, and in line with the scar theory of depression, the level of neuronal vulnerability waxes and wanes throughout life, depending on environmental influences (Ellis et al., 2011). Crucially, the differential susceptibility model also suggests that *those* individuals that have an increased vulnerability to additional stress are also the ones that are also most sensitive to *positive* environmental changes.

Positive environmental changes

This thesis provides evidence for a model in which CEM increases individuals' emotional vulnerability through altering brain structure, brain functioning, and negative self- and other-reflective processes. However, this thesis also suggests that individuals reporting CEM may also be especially sensitive to positive environmental changes and interventions, aimed at

reducing their cognitive and neuronal vulnerability. Here I will offer two suggestions for positive environmental changes and interventions for these individuals.

SOCIAL SUPPORT

Social support may be an important factor that may reduce CEM related adverse effects on neurobiology and cognition. The importance of social support in the aftermath of trauma is exemplified by the fact that postwar mental health in Nepalese child soldiers seemed to depend on the way their families and villages supported them (Kohrt et al., 2008). In villages where these former child soldiers were ostracized, they suffered continuously high levels of post-traumatic stress disorder. However, in villages that socially supported the former child soldiers, they experienced no more psychiatric distress than did their peers who had never gone to war. Social support may modulate the link between trauma and psychopathology through dampening stress related brain responses. For instance, social support during fMRI scanning has been found to reduce distress related brain functioning in healthy young adults (Eisenberger, Taylor, Gable, Hilmert, & Lieberman, 2007; Masten, Telzer, Fuligni, Lieberman, & Eisenberger, 2012), even when levels of social support were measured two years prior to scanning (Masten et al., 2012), suggesting a long-term impact of social support on brain responses to immediate stress.

Causal evidence for the importance of social support in the aftermath of trauma comes from animal studies showing that positive environmental changes during adolescence can *reverse* the impact of stress on neurobiology. In juvenile rats that had been exposed to in utero stress, enrichment increased their play behavior, emotionality, and anti-inflammatory cytokines interleukin 1beta (Laviola et al., 2004), and reversed the impact of in utero stress on prolonged corticosterone response to restrained stress (Morley-fletcher et al., 2003). The intriguing question is therefore whether social support also reverses CEM related brain structure and functioning in humans. This should be the subject of future studies. If social support indeed reverses the impact of CEM on cognition and the brain, then this will have important clinical implications. Therapists treating individuals with CEM could then focus (parts of) their treatment on increasing individuals' likelihood of receiving social support outside the treatment environment. Perhaps through interpersonal skills training, which has been found to be a good way to enhance the likelihood and the quality of social support (Uchino, 2009).

PSYCHOTHERAPY

The findings in this thesis point to maladaptive self- and other- referential processing as the core feature of CEM related dysfunctional emotional cognitive functioning. Therefore, individuals reporting a history of CEM may benefit especially from CEM focused psychotherapy that is specifically aimed

at reducing their negative cognitive schemas. This could be part of their interpersonal therapy, schema-based therapy, or cognitive (behavioural) therapy. In addition, the findings in thesis also suggest that individuals with a history of CEM may be especially sensitivity to *positive* stimuli and material, which should be further examined. If this is the case, than therapists should also focus their treatment on enhancing the accesibility of positive memories, feelings, and cognitions in individuals with CEM. Perhaps through training individuals ability to generate vivid mental images of future positive events (Blackwell et al., 2013).

Psychotherapy might be able to normalize neurobiology in patients (see for reviews Thomaes et al., submitted; Zantvoord et al., 2013). For instance, psychotherapy has been associated with increases in plasticity in the PFC (De Lange et al., 2008), and improved midline functioning (Furmark et al., 2002; Goldapple et al., 2004; Thomaes et al., 2012). These findings are in line with the suggestion that neurobiological alterations underlie an increased cognitive vulnerability/sensitivity. The question remains, however, whether extensive psychotherapy aimed at reducing negative self- and other referential processing in CEM similarly normalizes neurobiology in individuals with CEM. This should be the subject of future studies.

IMPLICATIONS

INCREASING AWARENESS OF THE IMPACT OF CEM

The findings in this thesis suggest that CEM has a sustained negative impact on cognition and neurobiology, and this impact is at least as severe as that of more physical forms of maltreatment. In the general public, however, the impact of CEM seems to be considerably under-estimated. This is exemplified by common aphorisms such as '*Sticks and stones break by bones, but words will never hurt me*'. Therefore our findings suggesting that '*words and neglect may hurt cognition and the brain'* warrant scientific and policital investments in order to increase societal awareness about the detrimental impact of CEM. It may therefore be important that the impact of CEM on cognition and the brain is distibuted through academic journals and within the media. Furthermore, the effects of CEM could be incorporated in psychosocial education programs that discuss the effects of childhood abuse in schools, general health practictions, mental health institutions, hospitals, sports clubs and other institions relevant for psycho-social education.

SCREENING FOR CEM

Most cases of CEM are not identified as such by child protection agencies, and child protection agencies may only see 'the tip of the iceberg' of the total number of maltreated children (see introduction of this thesis). Our finding that CEM has a persistent negative impact on cognition and the brain underlines the importance of screening for a history of CEM. For instance, the notion of 'injury based' assessment of child physical and sexual maltreatment that is used by child protection agencies could be extended to the assessment of maladaptive self-schema's, in order to also assess

potential CEM (see also Yates & Wekerle, 2009). In addition, therapists should assess history of CEM in patients reporting physical and/or sexual abuse, and in patients with depressive and/or anxiety disorders without physical and sexual trauma. Additionally, our findings, together with those that most children that are reported to have CEM are *not* in relative placement (Trickett et al., 2009) stress that policies regarding relative placement for abused children should also incorporate CEM.

LIMITATIONS

There are several limitations that must be acknowledged. Here I will discuss some of the most pressing limitations that are related to all the studies in this thesis. Other limitations are discussed in the separate chapters of this thesis.

SELF-REPORTED CEM

All studies in this thesis relied on a retrospectivel recall when assessing history of CEM, and it is important to acknowledge the subjectivity of retrospective self-reported CEM. Self-reported CEM may be subject to biased recall and inflation, where patients with depression and/or anxiety may over-report histories of CEM, and healthy controls may under-report CEM histories (McNally, 2003). Although, CEM is more likely to be under- than over- reported (Hardt & Rutter, 2004). Furthermore, in the NESDA sample, current affective state did not moderate the association between CEM (as measured with the NEMESIS interview) and lifetime affective disorder (Spinhoven et al. 2010), indicating that recall of CEM may not be critically affected by current mood state. Furthermore, depressed women with emotional neglect histories are less prone to produce false memories on the Deese-Roediger, Mcdermott (DRM) task than depressed women with no emotional neglect and women with any type of maltreatment (Grassi-Oliveira et al., 2011).

Another important limitation of retrospective recall is that retrospective measures of self-report are most likely to identify the most severe cases of childhood abuse (Shaffer, Huston and Egeland, 2008). Therefore, reliance on a single method of self-report can overlook cases of moderate abuse. This may have led to an over-estimation of the impact of CEM on cognition and the brain. Future studies should therefore employ multiple childhood trauma measures in order to assess history of CEM.

We assessed history of CEM with the NEMESIS interview in chapters 2,4,5,6 (de Graaf et al., 2002; 2004). However, this particular measure has not yet been formally validated. The NEMESIS trauma interview is a semi-structured interview that assesses presence of maltreatment history (yes or no), frequency of the matreatment, and relationship with the perpetrator. A history of maltreatment (including emotional abuse and emotional neglect) according to the NEMESIS trauma interview has been associated with incidence and prevalence of psychiatric disorders, suggesting that the

NEMESIS trauma interview has good contruct validity (e.g. de Graaf et al., 2002; 2004; Wiersma et al., 2009; Hovens et al., 2010; Spinhoven et al., 2010).

We assessed history of CEM with the CTQ questionnaire in chapters 3 and 7 (Bernstein & Fink, 1998). The CTQ is a well-validated and reliable questionnaire (Thombs, Bernstein, Lobbestael, & Arntz, 2009), and the test-retest reliability of the CTQ subscales for emotional abuse and emotional neglect have been found adequate across different ranges of samples (i.e. College students, psychiatric patients, and convenience samples, Tonmyr, Draca, Crain, & Macmillan, 2011). The CTQ measures dimensional aspects (i.e. severity) of a history of childhood abuse. Presence or absence of a history of childhood abuse can be infererred from the CTQ using cutt-off scores (Bernstein & Fink, 1998). In this thesis CEM severity was based on scores indicating moderate to extreme scores on the emotional abuse and/or emotional neglect subscales. The CTQ and NEMESIS trauma interview have adequate correlations. In addition, the CTQ is more sensitive to a history of CEM when compared to the NEMESIS trauma interview (Spinhoven et al., in prep). Furthermore, it is important to note that the CTQ does not provide additional information on the frequency of the abuse, nor the relationship with the perpetrators. Therefore, future studies examining history of CEM should assess CEM using a both the CTQ, and NEMESIS interview in order to enhance the sensitivity of self-reported CEM, and to gain additional information about the maltreatment (Spinhoven et al., in prep).

Brain structures are part of brain networks

In this thesis we have investigated the impact of CEM on predominantly isolated brain structures such as the mPFC and the amygdala. However, brain structures are part of larger brain networks (Alexander-Bloch & Giedd, 2013). Although, we examined mPFC connectivity in chapter 6 of this thesis, this was only a post-hoc analysis, and not the main aim of that chapter. A better understanding of the impact of CEM on the structure and function of brain networks is vital in furthering our understanding of the pathophysiology of psychiatric disorders (Hulshoff Pol & Bullmore, 2013; Linden, 2012). For instance, in line with the findings in this thesis (Figure 1), CEM has a negative impact on resting state functional connectivity in self-processing and affect regulation networks in the brain (Van der Werff et al., 2012). Therefore, future studies should examine the impact of CEM on structural brain networks, and in the functioning of those networks during emotional brain functioning.

Cross sectional design

All studies in this thesis employ a cross-sectional design, and as such cannot be generalized to the intra-individual level (Kievit et al., 2011; Molenaar & Campbell, 2009). Furthermore, we cannot make inferences about the dynamics of CEM related alterations in cognition and the brain in

adults over time. We can only speculate about the relative stability of our findings in adults over time: perhaps CEM related cognition and brain alterations subside over time, and are therefore not found in elderly individuals. In addition, the second aim of this thesis was to investigate the mechanism through which CEM leads to psychopathology. However, because of our cross-sectional design we could not examine how predictive our findings are for the development of depression and anxiety in adulthood over time. For instance, we could not investigate whether reduced mPFC volume in healthy adults reporting CEM subsequently leads to the development of depression or anxiety disorders when these individuals are faced with life stressors. To overcome such limitations, future studies examining the impact of CEM on cognition and the brain in adults should incorporate longitudinal designs that utilize multiple scanning sessions.

CEM IS PART OF A NETWORK OF INTERRELATED RISK AND RESILIENCE FACTORS

In order to enhance the sensitivity and specificity of studies to understand the impact of CEM on the course of cognition and neurobiology, future studies should utilize multivariate statistical analyses (Goodyer, 2012). For instance, psychiatric disorders are not best seen as categorical states (i.e. you have them or not). Rather, psychiatric disorders are dimensional, dynamic and can best be described as networks of inter-related symptoms that influence each other over time (Borsboom & Cramer, 2013; Cramer, Waldorp, Van der Maas, & Borsboom, 2010). This may explain why there is considerable comorbidity between psychiatric disorders (Borsboom, Cramer, Schmittmann, Epskamp, & Waldorp, 2011). In line with the differential susceptibility model (Ellis et al., 2011), early life stress may similarly function as one of the nodes in a network of interrelated vulnerabilities and protective factors. These factors together impact someone's brain structure, brain functioning, and cognitive functioning. For instance, whereas an individual may have a certain vulnerable genotype, he or she may also exercise regularly. And, BDNF levels that are crucial for neural proliferation have been shown to be influenced by exercise (Cotman, 2002). Furthermore, even seasonal variations and the amount of daily sunlight seems to impact upon BDNF levels (Molendijk et al., 2012), suggesting that the climate in which an individual lives may also be an important node in the vulnerability/ protection network. Future studies should therefore incorporate a network model approach when examining the impact of CEM on cognition and the brain.

Conclusion

The findings in this thesis suggest that CEM is associated with a sustained negative impact on cognition, brain structure and brain functioning. Moreover, we found that the impact of CEM is at least as severe as that of physical and sexual abuse. These findings provide a crucial first step in our understanding of the detrimental impact of CEM on cognition and the brain, and may potentially explain why individuals with a history of CEM are reported to have behavioral and emotional problems in later life.

The finding that CEM in its own right has a persistant negative impact on cognition and the brain stresses the importance of screening for CEM. Child protection agencies need to actively screen for CEM in at risk children, and therapists should assess history of CEM in their patients.

Finally, it is crucial that the general public is made aware of the detrimental impact that CEM has on cognition and the brain. Increased societal knowledge will hopefully lead to better awareness, reports, and subsequent interventions for individuals with CEM. Potentially, and similarly to a reduction in the rates of physical and sexual abuse in the last 15 years (Gilbert, Widom, et al., 2009; see introduction of this thesis), increased societal awareness of the detrimental impact of CEM on cognition and the brain may even lead to a reduction in the rates of childhood emotional maltreatment.