CHAPTER 1: GENERAL INTRODUCTION

When you remember your childhood, what do you remember? Do you remember that your parents were always there for you, that they loved you? Do you remember that they gave you cuddles and chocolate milk when you had hurt yourself, or when you felt sad, or ill? Do you remember that they let you sleep in their bed when you were scared because you had a nightmare? Do you remember that your parents went to all your school performances, and all your sports games? One out of three adults, however, does not share these childhood memories. When they think back of their childhood, they remember that their parents used to curse at them when they were ill. Their parents used to ignore them when they had had a nightmare and were afraid. They may even remember being told that their parents wished that they were never born.

Childhood emotional maltreatment (CEM; emotional abuse and/or emotional neglect) is the most prevalent form of childhood abuse. However, of all forms of childhood abuse, CEM is also the most hidden, underreported and least studied form of abuse (Barnett, Miller-Perrin, & Perrin, 2005; Egeland, 2009; Gilbert, Widom, et al., 2009; Stoltenborgh, Bakermans-Kranenburg, & van Ijzendoorn, 2013; Trickett, Mennen, Kim, & Sang, 2009; Yates & Wekerle, 2009). Until now, most studies examining the effects of childhood abuse have focussed on more obvious forms of maltreatment such as physical and sexual abuse (see Hart & Rubia, 2012; McCrory, De Brito, & Viding, 2012). This focus on physical forms of abuse has led to extensive knowledge on the impact of physical and sexual abuse. Enhanced knowledge has led to better awareness, reports, and interventions for these individuals, and may be the reason why the rates of physical and sexual abuse seem to have dropped by 50% in the last 15 years in high-income western countries (Gilbert, Widom, et al., 2009). No such drop has been observed for CEM. Therefore, it is crucial to similarly investigate the impact of emotional maltreatment in childhood. This thesis aims to provide just that, by examining the long-term impact of CEM on cognition and the brain (i.e. brain structure and functioning).

CHILDHOOD MALTREATMENT

In 2009, more than 1600 children died as a consequence of childhood maltreatment in the USA (National Child Abuse and Neglect Data System (NCANDS, 2009). Childhood maltreatment, or child abuse, consists of any act, or series of acts by a parent or caregiver that results in the (potential for) harm, or threat of harm, to a child, and can be subdivided into abuse (i.e sexual, physical and emotional), and neglect (i.e. physical and emotional) (Gilbert, Widom, et al., 2009). In 82% of cases the parents or other caregivers are perpetrators of the abuse (US Department of Health and Human services). Between 1,5-5% of all children are referred to child protection agencies for any of these types of abuse in the UK, Canada, and the USA (Gilbert, Kemp, et al., 2009). In 2010, in the Netherlands, childhood

abuse was reported to child protection agencies in 3,4% of all children (Alink et al., 2011). However, self-reported rates of child abuse are much higher (Gilbert, Widom, et al., 2009; Stoltenborgh, Bakermans-Kranenburg, Alink, & van IJzendoorn, 2012; Stoltenborgh, Bakermans-kranenburg, Van Ijzendoorn, & Alink, 2013; Stoltenborgh, Bakermans-Kranenburg, et al., 2013). For instance, rates of self-reported childhood abuse were found to be 18.7%, amongst almost 2000 adolescents in the Netherlands (but dropped to 9.9% if stricter criteria were set) (Alink et al., 2011). In line, self-reported child abuse rates up to 35% have been reported across the world (see Gilbert, Widom, et al., 2009). Even though self-reported rates are subject to forgetting, suppression, and mood related biases, childhood abuse is generally more likely to be under-reported than over-reported (Brewin, Kleiner, Vasterling, & Field, 2007; Hardt & Rutter, 2004). Therefore, the actual rates of child maltreatment may be even higher than those reported here. In addition, the discrepancy between the child abuse rates reported by child protection agencies/informant studies and self-report/survey studies suggest that most incidences of child abuse are not reported to the authorities. Child protection authorities may only see the 'tip of the iceberg'.

Maltreated children often experience more than one type of maltreatment. For instance, depending on the classification used, between 36-91% of child protection service cases were classified as multiple types of abuse, with especially emotional abuse rarely occurring alone (1.2%; see Gilbert, Widom, et al., 2009). Similarly, amongst those adolescents reporting childhood abuse, nearly 50% reported multiple types of abuse (Alink et al., 2011). Furthermore, children exposed to one type of maltreatment are at high risk for another type of maltreatment. In addition, a single episode of maltreatment is highly related to repeated maltreatment, and frequency is positively associated with the severity of maltreatment (Dong et al., 2004; Edwards, Holden, Felitti, & Anda, 2003; Finkelhor, Ormrod, & Turner, 2007; Gilbert, Widom, et al., 2009). Finally, child abuse forms a prelude to the development of psychopathology in later life; 45% of all childhood onset and 30% of adult onset psychopathology is related to childhood maltreatment (Green et al., 2010).

CHILDHOOD EMOTIONAL MALTREATMENT

Emotional abuse and emotional neglect in childhood are both (potentially) harmful to a child's emotional and psychological needs (Egeland, 2009; Gilbert, Widom, et al., 2009). For instance, during childhood emotional neglect, a child may be abandoned, parents may be inattentive to the child's emotional developmental needs, or fail to provide for the child's psychological needs (Gilbert, Widom, et al., 2009). The definition of emotional abuse is subject to debate (e.g. Trickett et al., 2009; Trocmé et al., 2011). However, most definitions include any type of behaviour by the parents that conveys to a child that he/she is worthless, flawed, unloved, unwanted, endangered, or valued only in meeting another's needs, and that

may cause severe and persistent adverse effects on the child's emotional development (Egeland, 2009; Gilbert, Widom, et al., 2009). According to the American Professional Society on the Abuse of Children (APSAC, 1995), emotional abuse consists of parental blaming, belittling, degrading, intimidating, terrorizing, isolating, denying emotional responsibility or otherwise behaviour that is insensitive to the child's developmental needs, or can potentially damage the child emotionally, or psychologically. These last categories illustrate that there is considerable theoretical overlap between the definitions of emotional abuse and emotional neglect. For instance, the APSAC category 'isolating' that is used to describe emotional abuse includes: 'a caretaker's behaviour that persistently denies the child opportunities to meet needs for interacting and communicating with peers, or adults inside or outside the home' (APSAC, 1995). In addition, the APSAC category 'denying emotional responsibility' that is used for the definition of emotional abuse includes: 'the caretakers behaviour that ignores the child's attempts and needs to interact (failing to express affection, caring, and love for the child), and show no emotion in interactions with the child' (APSAC, 1995). These two descriptions are both omissive in nature, and can therefore also be described as emotionally neglectful. In line with this theoretical overlap, emotional abuse rarely occurs alone (1-2%), and very high co-occurrence between emotional abuse and emotional neglect has been reported (i.e. 91%; Trickett et al., 2009). For these reasons, it has been suggested that emotional abuse and emotional neglect together form Childhood Emotional Maltreatment (CEM); any act of omissive (emotional neglect), or comissive (emotional abuse) behaviour that is potentially harmful to a child's emotional and psychological development (Egeland, 2009; Trocmé et al., 2011; Yates & Wekerle, 2009).

PREVALENCE OF CEM

Emotional maltreatment in childhood largely occurs within the family (i.e. 81% of perpetrators of emotional abuse are the parents (Gilbert, Widom, et al., 2009; Trickett et al., 2009). Therefore, it has been suggested that CEM may represent the core component of a hostile/hazardous family environment, within which other types of abuse may also occur (Hart, Brassard, Binggeli, & Davidson, 2001). Theoretically, this would make CEM the most prevalent type of childhood abuse. Indeed, large meta-analyses of studies published between 1980 and 2008 indicated prevalence rates as high as 36,2% for self-reported emotional abuse, whereas prevalence rates were 12.7% and 22.6% for self-reported sexual or physical abuse respectively. In line, worldwide prevalence rates suggested rates up to 33% for self-reported emotional abuse and up to 15.4% for self-reported neglect (physical and emotional) (Gilbert, Widom, et al., 2009). In line, a recent meta-analysis indicated a prevalence rate of 18.4% for emotional neglect amongst the few studies that examined childhood emotional neglect between 1980 and 2008 (Stoltenborgh, Bakermans-Kranenburg, et al., 2013). Indeed, emotional neglect was one of the most often reported types

of abuse in 2000 adolescents in the Netherlands (Alink et al., 2011). However, it should be noted that neglect has received far less scientific attention when compared to the other types of abuse, and actual prevalence rates for neglect may be higher (Gilbert, Widom, et al., 2009; Stoltenborgh, Bakermans-Kranenburg, et al., 2013).

OFFICIAL IDENTIFICATION OF CEM

Child protection agencies seldom identify children as having experienced CEM (Gilbert, Widom, et al., 2009). Indeed, informant studies based on the judgement of clinical professionals indicated a prevalence rate of 0.3% for childhood emotional abuse (Stoltenborgh et al., 2012). In addition, Tricket et al., (2009) reviewed cases of child abuse reported by the Los Angeles County Department of Children and Family Services (DCFS). According to the DCFS, the rates of CEM (i.e. emotional abuse) were 8.9% in a sample of nearly 300 children with documented histories of childhood maltreatment. However, when using the APSAC definition of emotional abuse, the rates of CEM increased to 48.4% of all children in the maltreated sample. Furthermore, emotionally abused children were more likely to have more frequent and more different types of maltreatment, although, they were less likely to be in relative placement compared with children that had experienced physical or sexual abuse (Trickett et al., 2009). Together with the fact that child protection agencies only see 'the tip of the iceberg', this underreporting of CEM indicates that most children with a history of CEM are not identified as such.

Lower identifications of CEM compared to physical and sexual abuse may be explained by the fact that child protection agencies are discouraged to identify more than one form of abuse (Gilbert, Kemp, et al., 2009; Gilbert, Widom, et al., 2009), and the effects of CEM are not as easily identifiable as those of more obvious forms of maltreatment (Egeland, 2009). Another reason for this underreporting of CEM by child protection agencies may be that it is assumed that the effects of CEM are less severe than those of physical and sexual abuse (Egeland, 2009; Trickett et al., 2009).

THE CONSEQUENCES OF CEM ON BEHAVIOUR

Childhood emotional maltreatment has a persistent adverse impact on a wide range of behavioural and emotional functioning (Egeland, 2009; Gilbert, Widom, et al., 2009; Rohner, 2004; Wekerle, 2011; Yates & Wekerle, 2009). For instance CEM (i.e. emotional abuse) is related to a cascade of behavioural problems directed towards the self, such as problems with impulse control, anger, eating disorders, physical self-abuse, suicidal behavior, and alcohol abuse (Hart, Bingelli, & Brassard, 1997). Emotional maltreatment in childhood is also related to problems in interpersonal functioning, such as attachment problems, low social competency, non-compliance, sexual maladjustment, dependency, aggression/violence, and delinquency/criminality (Hart, Bingelli, & Brassard, 1997). In addition,

individuals reporting CEM are less likely to be accepted by peers, unpopular, and more socially withdrawn (Egeland, 2009; Shaffer, Yates, & Egeland, 2009; Trickett et al., 2009; Wright, Crawford, & Del Castillo, 2009; Yates & Wekerle, 2009). Moreover, CEM has also been linked to relational problems and dating violence (Wekerle, 2011). In addition, CEM has been linked with physical problems such as failure to thrive, somatic complaints, poor adult health, and high mortality (Hart, Bingelli & Brassard, 1997). Finally, CEM is related to problems with intellectual behaviour/functioning. For instance CEM has been related to learning problems (Hart et al., 1997), reduced socioeconomic competence (Shaffer et al., 2009), impaired spatial working memory (Majer, Nater, Lin, Capuron, & Reeves, 2010), poorer verbal fluency, and reduced cognitive flexibility (Savitz, Van der Merwe, Stein, Solms, & Ramesar, 2008).

THE CONSEQUENCES OF CEM ON EMOTIONAL COGNITIVE FUNCTIONING

Emotional maltreatment in childhood is similarly related to a cascade of negative outcomes on emotional cognitive functioning. During episodes of CEM, negative attitudes are provided to the child (e.g; '"You are such a stupid child. You are worthless"; see Rose & Ambramson, (1992). Emotionally abused children may incorporate these negative cognitions into negative self-inferential styles, dysfunctional self-attitudes, and low self-worth (Beck, 2008; Rose & Ambramson, 1992). Increased negative self-associations, in itself, are hypothesized to enhance (negative) bias and recall when engaged in new situations, and when retrieving memories (Beck, 2008). Abused individuals, therefore, may get caught in a negative loop, where CEM may enhance negative biases, which may result in more frequent and more intense negative experiences, which in turn may enhance negative self-associations, etc. Due to this process, emotionally abused individuals may be more vulnerable to develop and/or maintain a depressive and/or anxiety disorder (Beck, 2008).

In line with this theory, CEM is related to enhanced negative self-cognitions, low self- esteem, negative life views, emotional instability, emotional unresponsiveness, and emotion dysregulation (Alloy, Abramson, Smith, Gibb, & Neeren, 2006; Egeland, 2009; Gibb & Abela, 2008; Gibb & Alloy, 2006; Gibb et al., 2001, 2007; Gibb, Schofield, & Coles, 2009; Gibb, 2002; Hart, Bingelli & Brassard, 1997; Kim & Cicchetti, 2010; Shaffer, Yates, & Trickett et al., 2009 Steinberg, Gibb, Alloy, & Abramson, 2003; Wright, Crawford, & Del Castillo, 2009; Yates & Wekerle, 2009). In addition, negative self-cognitions mediated the development of non-endogenous major depression in children reporting CEM on a 2.5 year follow up (Gibb et al., 2001).

Indeed, CEM is a strong predictor of psychopathology in later life. CEM has been specifically associated with depression and anxiety in adulthood (Hart et al., 1997; Iffland, Sansen, Catani, & Neuner, 2012; Spinhoven et al., 2010; Wright et al., 2009). In addition, CEM has been associated with borderline personality disorder (Hart et al., 1997), elevated levels of PTSD (Wekerle,

2011), and dissociative symptoms (Wright et al., 2009). Compared to physical and sexual abuse, CEM has a stronger relationship with depression and anxiety disorders (Iffland et al., 2012; Spinhoven et al., 2010). Finally, the link between physical abuse and depression and anxiety in later life appears to be fully explained by a concurrent history of CEM (Iffland et al., 2012; Spinhoven et al., 2010), which is in line with the idea that CEM is the core component of negative family environments in which other types of abuse may co-occur.

SUMMARY

Taken together, CEM has a persistent negative impact on emotional behavior and cognitions, and is a potent predictor of depressive and anxiety disorders in later life. However, it is unclear how CEM leads to the development of depressive and anxiety disorders in adulthood. Examining the mechanisms that make-up this aetiological chain is important in order to identify possible targets for therapeutic interventions aimed at individuals reporting CEM. Therefore, in this thesis, we not only aimed to further examine the impact of CEM on emotional cognitive functioning ('cognition') and the brain (i.e. brain structure and functioning). We also examined whether changes in cognition and/or the brain were related to the development of depressive or anxiety disorders. To this end, we examined whether the impact of CEM on cognition and the brain was especially pronounced in patients with a depression and/or anxiety disorder (chapters 2,4,5,6,7), and we examined whether CEM-related cognitions and emotional brain functioning were associated with more psychiatric distress in chapters 2, 3 and 7.

NOISE AND EFFECT

Distinguishing the impact of CEM from other factors that may influence child development is not as straightforward as it may seem. Emotional maltreatment in childhood often co-occurs with other forms of childhood abuse, exposure to other stressful events, as well as co-morbid depressive and/or anxiety disorders (Egeland et al., 2009). Each of these factors in itself may also influence cognition and the brain (i.e. brain structure, and/or functioning). It is therefore crucial that when examining the impact of CEM on cognition and the brain, that these risk factors are also considered. Only then can the impact of CEM be disentangled from the impact of other confounding factors on cognition and the brain, such as other types of maltreatment, recent stressful life events, and comorbid depressive and/or anxiety disorders. Therefore, we examined the impact of CEM on cognition within the Netherlands Study of Depression and Anxiety (NESDA) sample (N=2981) in chapter 2. Additionally, we examined the impact of CEM on the brain within the NESDA-MRI (magnetic resonance imaging) sample (N=301) (Penninx et al., 2008) in chapters 4, 5 and 6. Because of the large number of psychosocial variables that were assessed, and the considerable sample

sizes in NESDA, we had enough power to control for various potential confounding factors when we investigated the impact of CEM on cognition and the brain.

The Netherlands study of Depression and Anxiety

The NESDA is an ongoing multi-center longitudinal cohort study designed to examine the long-term course and consequences of depressive and anxiety disorders. The NESDA assessed a wide range of biological, psychosocial, emotional, and cognitive factors in a very large sample (N=2981; 66.5% female; age 18-57) of patients with depression and/or anxiety disorder, and healthy controls (see Penninx, 2008 for a complete description of the sample, and the methods used). Recruitment for the NESDA sample took place in the general population, general practices, and in mental health care institutions in order to recruit individuals reflecting various settings and developmental stages of psychopathology. Inclusion criteria in the NESDA study were: a current (during the past month) or past (lifetime) DSM-IV diagnosis of depressive disorder [DEP; Dysthymia, Major Depressive Disorder (MDD), and/or anxiety disorder (ANX; i.e. Generalized Anxiety Disorder, Panic Disorder with or without agorophobia, Social Phobia and/or Agoraphobia without panic disorder). Non-clinical (Healthy) controls without a present or past diagnosis were also included in the NESDA. Because of the specific focus on depression and/or anxiety disorders, individuals with an apparent clinical diagnosis of other disorders, such as psychotic disorder, bipolar disorder, or severe addiction disorder were excluded in the NESDA.

The NESDA MRI study

A subset of the NESDA sample was selected to undergo Magnetic Resonance Imaging (MRI) as part of the NESDA MRI study. The NESDA MRI study included healthy controls, and patients with current (<6 months) DSM-IV major MDD and/or ANX. Eventually, 301 native Dutch-speaking participants (235 patients and 66 HCs, 66% female, age range: 18-57 years) underwent MRI scanning. During MRI scanning, structural scans were obtained to investigate gray matter volume and white matter integrity. In addition, functional (f)MRI scanning was obtained during emotional functioning (i.e. emotional face processing and emotional memory), during basic cognitive functioning (i.e. visuo spatial planning), and during rest when participants did not perform a task (i.e. resting state). In this thesis, we examined the impact of CEM within the NESDA MRI sample on brain structure (chapter 4), and brain functioning during emotional tasks in chapter 5 and 6 (i.e. emotional face processing, and emotional memory).

This thesis

This thesis is divided into three sections. We examined the long-term impact of CEM on cognition in section 1. Section 2 investigates the impact of CEM on brain structure; whereas CEM related brain functioning is examined

in section 3. In the following section, I will provide a theoretical background to the specific studies in this thesis. Therefore, I will only describe those studies that examined the impact of CEM on cognition and the brain (structure and functioning) that were published or in press before the publication of the first chapters in this thesis (2010). More recent studies that examined the impact of CEM on cognition and the brain are considered in the general discussion of this thesis.

SECTION 1: THE IMPACT OF CEM ON COGNITION

In section 1 we examined the impact of CEM on self-cognitions, and on autobiographical memory processing.

THE IMPACT OF CEM ON SELF-COGNITIONS.

Emotional maltreatment leads to the development of negative explicit self-cognitions. Explicit self-cognitions are thought to influence deliberate and controlled behavior. Spontaneous and unintentional behavior, on the other hand, is assumed to be under the influence of more automatic self-associations (Gawronski & Bodenhausen, 2006). Automatic self-associations (e.g. 'I - worthless') become activated directly in response to certain stimuli or events (e.g. being yelled at), and are therefore hypothesized to play an important role in immediate/short term affective behavior (e.g., crying), and in the development and maintenance of depressive and/or anxiety disorders (Gawronski & Bodenhausen, 2006; Gawronski, Hoffman, & Wilbur, 2006; Haeffel et al., 2007). In line with this theory, in soldiers deployed to Iraq, post-deployment automatic self-vulnerability associations explained unique variance in current PTSD symptoms (Engelhard, Huijding, van den Hout, & de Jong, 2007).

However, no study had examined (dysfunctional) automatic self-associations in individuals reporting a history of CEM. Therefore, in chapter 2, we examined automatic and explicit self-cognitions in individuals reporting childhood abuse. We investigated whether CEM had a stronger relationship with these cognitions when compared to physical and sexual abuse. We also examined whether negative automatic and explicit self-cognitions were especially pronounced in those with depression and anxiety disorders, compared to healthy controls. Finally, we examined whether automatic and explicit self-cognitions mediated the link between CEM and depressive and anxiety symptoms.

THE IMPACT OF CEM ON AUTOBIOGRAPHICAL MEMORY PROCESSING

Negative self-associations bias attention towards more negative interpretations when retrieving memories of, and when engaged in interpersonal interactions, resulting in more negative memories (Beck, 2008). In response to these memories, emotionally abused individuals may try to avoid thinking about these distressing thoughts or memories. In line with this idea, emotionally maltreated adults have been characterized by

avoidant coping styles in which emotional inhibition strategies such as thought suppression are utilized in order to avoid experiencing distressing thoughts or memories (Krause, Mendelson, & Lynch, 2003). However, attempts to suppress a certain memory or thought, may paradoxically lead to increase in the occurrence of that memory or thought ('intrusions' Wegner, Schneider, Carter, & White, 1987; Wenzlaff & Wegner, 2000). Thus, despite this seemingly useful coping strategy, an enhancement of intrusions of distressing material may occur. This is especially prominent in individuals with an avoidant coping style (Geraerts & McNally, 2008; Wenzlaff & Wegner, 2000). In line with this theory, emotional inhibition styles, such as thought suppression, are associated with more depressive and anxious symptoms (Reddy, Picket, & Orcutt, 2006; Rosenthal, Polusny, & Follette, 2006; Spinhoven & van der Does, 1999). Also, emotion inhibition tendencies mediated acute psychological distress in emotionally maltreated individuals (Krause, et al., 2003).

So far, studies that examined suppressive coping styles in individuals reporting CEM have utilized self-report questionnaires in order to examine self-reported emotion inhibition tendencies or styles. Therefore, it was unclear what the exact consequences of these emotion inhibition styles (i.e. thought suppression) were on the intrusion of autobiographical memories in individuals reporting CEM. Therefore, and using a thought suppression task, in chapter 3, we investigated the impact of varying degrees of CEM on autobiographical memory intrusions in a sample of 83 healthy psychology students (mean age 19.7 $\pm$ 1.93 years) reporting No Abuse (n=24), Low CEM (n=22), Moderate CEM (n=20), and Severe CEM (n=16). We examined autobiographical memory intrusions during active suppression, and when no longer instructed to actively suppress positive and negative autobiographical memories. We also explored whether intrusions of autobiographical memories during the thought suppression task were related to self-reported distress.

SECTION 2: THE IMPACT OF CEM ON BRAIN STRUCTURE

THE IMPACT OF CEM?

To examine the causal impact of CEM on the brain, longitudinal studies are required. However, it is unethical to study brain development in maltreated children over time without interfering in their home environment. Therefore, the studies in this thesis examined the impact of CEM on the brain use cross-sectional designs. However, these designs hamper the causal interpretations of the potential impact that CEM has on the brain.

A potential solution to this problem may come from experimental studies in animals. Since, pre-clinical studies can investigate the impact of early life stress on neurobiology over time. Furthermore, compared to humans, rats and primates are characterized by a similar anatomical organization of cortical–striatal loops in the brain (Berendse, Galis-de Graaf, &

Groenewegen, 1992), and have similar stress and anxiety brain mechanisms (Myers-Schulz & Koenigs, 2012; Phillips, Drevets, Rauch, & Lane, 2003).

Most animal studies that examined the impact of early life stress on neurobiology utilize paradigms that closely resemble CEM, or at least the aspect of emotional neglect. For instance, during maternal separation, pups are separated from their mother for certain periods of time (Sánchez, Ladd, & Plotsky, 2001). Therefore, animal studies may provide an important preclinical extension/corroboration to the findings of early life stress in humans, and are thus highly informative in order to further our understanding of the causal impact of CEM on neurobiology over time. Hence, in order to consider the potential long-term causal impact of CEM on the brain, it is important to link the findings on the impact of CEM on the brain (structure and functioning) as described in this thesis, to those found in animals.

THE IMPACT OF EARLY LIFE EMOTIONAL STRESS ON NEUROBIOLOGY

Animal studies using maternal separation and isolation rearing, suggest that emotional stress in early life is associated with alterations in neural morphometry of the animal brain. These alterations include reduced -dendrite length, -branching, -density, and suppression of neurogenesis, predominantly in the limbic structures (amygdala, hippocampus), and the (medial) prefrontal cortex (PFC) (Arnsten, 2009; Lupien et al., 2009; Radley et al., 2004; Sánchez, Ladd, & Plotsky, 2001). Therefore, these pre-clinical studies suggest that CEM may have a similar detrimental impact on neuro-anatomy in humans. However, at the time of the start of this thesis, studies examining the impact of early life stress on brain morphology focussed only on physical and sexual abuse. The impact of CEM on brain structure was unknown.

THE IMPACT OF CHILDHOOD PHYSICAL AND SEXUAL ABUSE ON THE BRAIN

In line with pre-clinical studies, studies examining the impact of childhood physical and/or sexual abuse on brain structures in adulthood indicated a negative impact on gray matter volume in the midline structures of the prefrontal cortex (PFC) and the limbic system (Amygdala, and hippocampus). For instance, reductions in (medial) PFC volume were found for adults reporting sexual abuse (Andersen & Teicher, 2008), physical abuse (Tomoda et al., 2009), and multiple types of abuse (Cohen et al., 2006; Kitayama, Vaccarino, Kutner, Weiss, & Bremner, 2005; Treadway et al., 2009). Furthermore, Anterior Cingulate Cortex (ACC) reductions were found for physical abuse (Tomoda et al., 2009), and multiple types of abuse (Cohen et al., 2006; Kitayama et al., 2005; Treadway et al., 2009). Interestingly, (medial) PFC reductions were most prominent if the sexual abuse occurred between ages 14-16 years (Andersen & Teicher, 2008). Hippocampal volume reductions were found in individuals reporting sexual and/or physical abuse

(Bremner et al., 1997; Stein, Koverola, Hanna, Torchia, & McClarty, 1997; Vythilingam et al., 2002), and multiple types of abuse (Driessen et al., 2000; Hedges & Woon, 2011; Kitayama, Vaccarino, Kutner, Weiss, & Bremner, 2005; Vermetten, Schmahl, Lindner, Loewenstein, & Bremner, 2006). Hippocampal volume reductions were most prominent if the abuse occurred at age 3-5 (Andersen & Teicher, 2008). Finally, amygdala volume reductions are reported in patients reporting multiple types of abuse (Driessen et al., 2000; Kitayama, Vaccarino, Kutner, Weiss, & Bremner, 2005; Vermetten, Schmahl, Lindner, Loewenstein, & Bremner, 2006).

The impact of CEM on the Brain

Studies examining the impact of early life stress in humans suggest alterations in grey matter volume of the midline structures of the PFC (mPFC, ACC), hippocampus, and amygdala. In line with the idea that CEM may impact the brain, reduced density of whiter matter tracts in the left superior temporal gyrus, cingulum bundle of the left hippocampus, and the left body of the fornix has been reported in young adult patients reporting CEM (Choi, Jeong, Rohan, Polcari, & Teicher, 2009). However, it was unknown whether CEM was related to altered grey matter structure of the (medial) PFC, and limbic system in adulthood. Furthermore, it was unknown whether CEM related brain alterations persisted into adulthood; the long-term impact of CEM on brain structure was unknown. Therefore, in chapter 4, we examined the long-term impact of CEM on brain structure. Using whole brain voxel based morphometry (VBM) and MRI, we examined whether patients and controls from the NESDA study reporting CEM showed differential brain anatomy in comparison with patients and controls that have not experienced any type of abuse in childhood. We also investigated whether brain alterations related to CEM were especially pronounced in individuals with a current depression and/or anxiety disorder, compared to healthy controls.

Section 3: The Impact of CEM on Brain Functioning

The impact of physical and/or sexual abuse on brain functioning

The midline structures of the PFC (ACC, mPFC), and limbic system (i.e. amygdala and hippocampus) are crucial for the processing and regulation of emotion, emotional behaviour, self- and other- referential thinking, and (emotional) memory functioning (Cardinal et al., 2002; den Ouden, Frith, Frith, & Blakemore, 2005; Milad et al., 2009; Radley et al., 2008; Whalen, 2007). Indeed, physical and/or sexual abuse have been linked with altered midline PFC and limbic brain functioning during traumatic script driven imagery (Bremner et al., 1999; Lanius et al., 2003; Schmahl, Vermetten, Elzinga, & Bremner, 2004; Shin et al., 1999), emotion processing (Bremner, Vythilingam, Vermetten, Vaccarino, & Charney, 2004), emotional memory (Bremner et al., 2003), fear conditioning (Bremner et al., 2005), working

memory processing (Raine et al., 2001), and during emotional face processing in young adults reporting multiple types of abuse (Taylor et al., 2006).

It was unknown whether CEM was similarly related to altered brain functioning in these regions during emotion processing, emotional memory and stress response. Therefore, in section 3 of this thesis, we examined the neural correlates of CEM during emotion processing (chapter 5), emotional memory (chapter 6), and interpersonal stress (chapter 7). In all these studies, we also examined whether CEM related neural responses were especially altered in individuals with a depressive and/or anxiety disorder, when compared to healthy controls.

THE NEURAL CORRELATES OF CEM DURING EMOTION PROCESSING.

In the context of chronic CEM, adequately responding to facial expressions is an important skill. Detecting when a parent is in a bad mood may help a child to avoid a negative confrontation with that parent, for example. However, over time, this adaptive response may lead to a persistent vigilance for negative facial expressions (Gibb et al., 2009). The amygdala is an important brain region involved in the primary processing of emotional faces, and plays a crucial role in salience detection, fear conditioning and emotional memory (Bremner et al., 2005; Davis & Whalen, 2001; Todorov & Engell, 2008; Onur et al., 2009). In addition, maternal deprivation is associated with a lasting enhancement of contextual and cued fear conditioning (Oomen et al., 2010). In line with the findings of persistent vigilance in animals, greater left amygdala activation during the processing of negative emotional faces was observed in a small sample of youths who experienced severe emotional and physical neglect in foster care or orphanages (Maheu et al., 2010). However, the long-term impact of CEM on brain functioning during emotion processing was unknown. Therefore, in chapter 5, we examined the neural correlates of CEM during emotional face processing in adults reporting CEM.

THE NEURAL CORRELATES OF CEM DURING EMOTIONAL MEMORY

Individuals with CEM are characterized by negative self-cognitions. Negative self-associations bias attention towards negative information about the self and others when engaged in stressful interpersonal situations, and when retrieving memories of such situations (Beck, 2008). The mPFC and limbic system are crucial for emotional memory functioning. However, it was unknown whether individuals reporting CEM are also characterized by differential functioning in these regions during emotional memory functioning. Therefore, in chapter 6 of this thesis, we examined the neural correlates of CEM during the encoding and recognition of positive, negative, and neutral words.

THE NEURAL CORRELATES OF CEM DURING INTERPERSONAL STRESS.

Chronic parental rejection (active and/or passive) can be considered as a core aspect of CEM. Social (peer) rejection, ranging from active isolation to passively ignoring a person, has been found to induce a higher sensitivity towards future rejection (de Wall & Bushman, 2012). Along these lines, individuals reporting CEM may be especially sensitive to (perceived) social rejection. Individuals high in rejection sensitivity have a tendency to expect, perceive, and overreact to social rejection, and show enhanced distress and related neural responses to social rejection in the lab (de Wall & Bushman, 2012). Furthermore, rejection sensitivity (both behaviourally and in terms of brain responses) is positively related to the development and maintenance of depression and social anxiety symptoms (Rosenbach & Renneberg, 2011). Therefore, enhanced distress and neural responses to (perceived) social rejection may be one of the mechanisms through which a history of CEM may predispose individuals to the development of depressive and anxiety disorders in later life. However, the impact of social rejection on individuals reporting CEM was unknown. Therefore, in chapter 7, we examined the impact of CEM on brain responses during social exclusion in a sample of 46 young adults. This sample consisted of 26 out- and inpatients reporting severe CEM who were in treatment at a center for youth specialized mental health care (mean age=18.31 years, SD=1.23; 6 males) and 20 healthy controls (mean age=18.85, SD=1.95; 6 males) reporting no-moderate CEM.