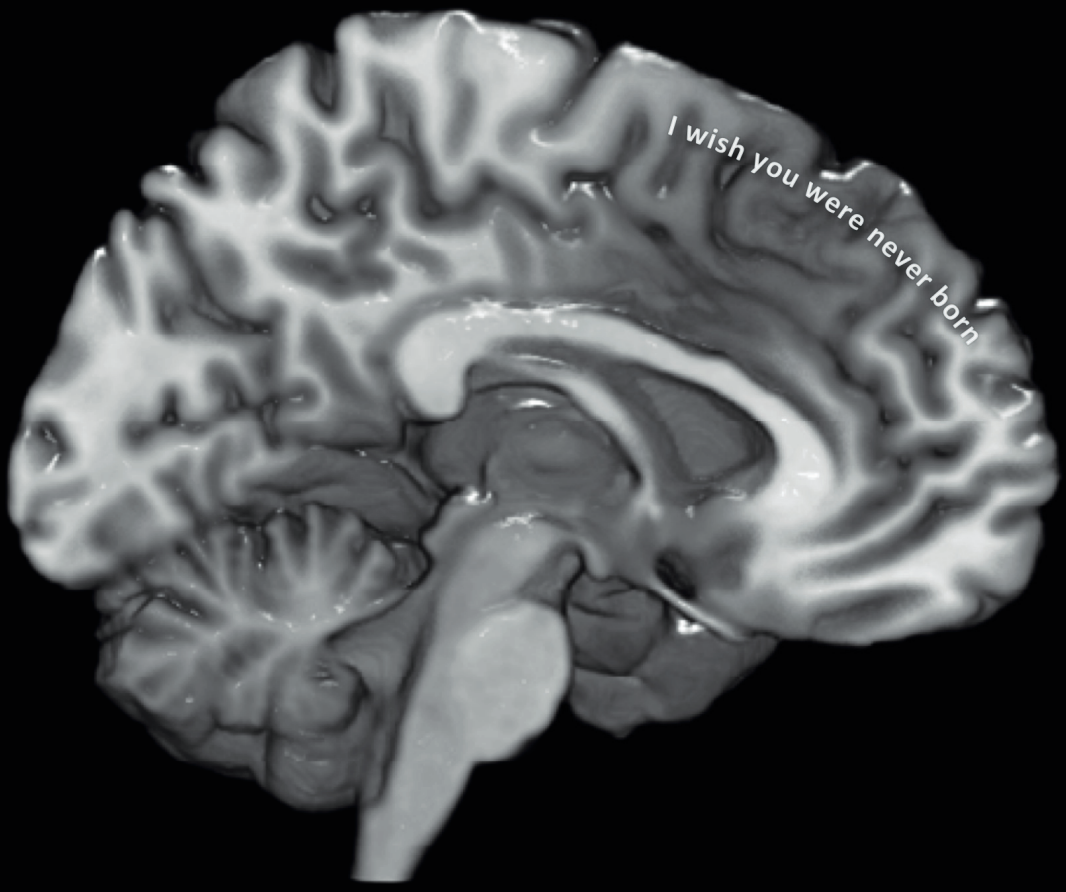
Childhood Emotional Maltreatment:

Impact on Cognition and the Brain



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CHILDHOOD EMOTIONAL MALTREATMENT:

IMPACT ON COGNITION AND THE BRAIN.

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'When I remember my childhood pains, I do not think about broken bones, hurt knees, swollen ankles; I remember the pain of being excluded, rejected, isolated'
S. Fry, 1997, Moab is my Washpot.

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Contents

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.

SECTION 1: THE IMPACT OF CHILDHOOD EMOTIONAL MALTREATMENT ON COGNITION

Chapter 2: Child abuse and negative explicit and automatic self-associations: the cognitive scars of emotional maltreatment.

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ABSTRACT

Individuals reporting Childhood Abuse (CA) (i.e., emotional neglect, emotional, physical and sexual abuse) are marked by increased explicit (i.e. self-reported) negative self-associations, and an increased risk to develop depression or anxiety disorders. Automatic self-associations might play an important role in the development and maintenance of affective disorders after exposure to CA, since automatic associations are assumed to be involved in uncontrolled (spontaneous) affective behavior. This study examined whether individuals reporting a history of CA show stronger automatic (and explicit) self-depression and/or self-anxiety associations than individuals who report no CA in a large cohort study (Netherlands Study of Depression and Anxiety (NESDA), N = 2981). The Implicit Association Test (IAT) was utilized to assess automatic self-depression and self-anxiety associations. We found that CA was associated with enhanced automatic (and explicit) self-depression and self-anxiety associations. Additionally, when compared to physical and sexual abuse, Childhood Emotional Maltreatment (CEM; emotional abuse and emotional neglect) had the strongest link with enhanced automatic (and explicit) self-depression and self-anxiety associations. In addition, automatic and explicit negative self-associations partially mediated the association between CEM and depressive or anxious symptomatology. Implications regarding the importance of CA, and CEM in particular will be discussed.

INTRODUCTION

Childhood abuse (CA) (e.g. emotional neglect and emotional, physical or sexual abuse) is a widespread phenomenon with incidence rates between 3-32% in the general population (Brown, Cohen, Johnson, & Salzinger, 1998; Briere & Elliott, 2003). Converging evidence in children, adolescents and adults indicates that CA can have a chronic impact on emotional functioning (Alloy, Abramson, Smith, Gibb, & Neeren, 2006; Silverman, Reinherz, & Giaconia, 1996). This is supported by associations between self-reported CA and the enhanced risk to develop both depressive (Agid et al., 1999; Kessler, Avenevoli, & Ries Merikangas 2001; Weiss, Longhurst, & Mazure, 1999) and/or anxiety disorders in later life (Gibb, Chelminsky, & Zimmerman, 2007; Hovens et al., 2010; Kendler et al., 2000; Kessler, Davis, & Kendler, 1997; Levitan, Rector, Sheldon, & Goering, 2003; Safren, Gershuny, Marzol, Otto, & Pollack, 2002; Spinhoven et al., 2010).

Experiences of CA have been suggested to lead to (an increase in) negative self-associations such as negative (self-) inferential styles, dysfunctional (self-)attitudes, and low self-worth (Beck, 1967; Beck, 2008). This is corroborated by numerous studies linking CA to enhanced negative self-associations (Alloy et al., 2006; Gibb, 2002; Jacobs, Reinecke, Gollan, & Kane 2008; Rose & Abramson, 1992). Furthermore, these increased negative self-associations, in itself, are hypothesized to enhance (negative) bias and recall when engaged in new situations, and when retrieving memories. Abused individuals, therefore, may get caught in a negative loop, where CA may enhance negative biases, which may result in more frequent and more intense negative experiences, which in its turn may enhance negative self-associations, etc. Due to this process, abused individuals may be more vulnerable to develop and/or maintain a mood and/or anxiety disorder (Beck, 2008).

It has been argued that childhood emotional abuse may be more strongly related to negative self-associations than childhood sexual and/or physical abuse, since during emotionally abusive episodes negative self-associations are explicitly handed to the child (for example '*you are such a stupid child, you are worthless'* see Rose & Abramson, 1992). This is corroborated by an accumulating number of studies indicating that childhood emotional abuse is more strongly related to negative cognitive styles (dysfunctional self-attitudes and negative (self-) inferential styles) than childhood sexual or physical abuse (Alloy, Abramson, Smith, Gibb, & Neeren, 2006; Gibb, 2002; Gibb, Abramson, & Alloy, 2004). Moreover, Gibb et al. (2001) found that, in healthy college freshmen, reported childhood emotional (and not physical or sexual) abuse was related to episodes of non-endogenous major depression and hopelessness depression during a 2.5 year follow up. More importantly, these relations were fully mediated by the presence versus absence of negative cognitive styles, which is indicative of the important role that negative self-associations play in predisposing an individual to the development of psychopathology.

Cognitive functioning is often divided into two distinct mental processes; propositional and automatic processes (Chaiken &Trope, 1999; Gawronski & Bodenhausen, 2006; Haeffel et al., 2007). Propositional processes are characterized by evaluative judgments (explicit cognitions), which are based on syllogistic inferences about the stimulus or event (e.g. I am being criticized; I know I made a mistake, thus I am inadequate). These explicit cognitions are thought to mainly influence deliberate and controlled behavior (Gawronski & Bodenhausen, 2006), and have been shown to be good predictors of long-term depressive and anxious symptoms (Haeffel et al., 2007; Engelhard, Huijding, van den Hout, & de Jong, 2007). Explicit cognitions can be measured with self-report instruments such as the Cognitive Style Questionnaire (CSQ) (see Haeffel et al., 2008). So far, studies examining the link between CA and enhanced negative self-associations are based on explicit (self-reported) self-associations (Alloy et al., 2006; Gibb et al., 2001; Gibb, 2002; Gibb, Alloy, Abramson, & Marx, 2003; Gibb et al., 2004; Gibb & Abela, 2008; Wright, Crawford, & Del Castillo, 2009). However, self-report measures can be prone to bias and distortion (e.g. McNally, 2001). For instance, individuals with a current depression might over report their negative self-associations, whilst individuals without a current depression might underreport their negative self-associations. Moreover, explicit cognitions are, due to their dependence on syllogistic inferences, controlled by conscious effort, thus an individual can override an initially negative association via conscious effort (e.g. I am being criticized; However, I know I did not make a mistake, thus I am not inadequate).

Automatic associations, on the other hand, are thought to be spontaneous and unintentional. 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 automatic affective behavior (e.g., crying) (Gawronski & Bodenhausen, 2006; Gawronski, Hoffman, & Wilbur, 2006; Haeffel et al., 2007). This is corroborated by findings that automatic self-worth associations predicted immediate affective reactions to a lab stressor, whilst explicit self-worth associations are predictive of depressive symptomatology on the long-term (Haeffel et al., 2007). Similarly, in soldiers deployed to Iraq, post-deployment automatic self-vulnerability associations explained unique variance in concurrent PTSD symptoms, while explicit associations were also predictive of long-term PTSD symptomatology (Engelhard, Huijding, van den Hout, & de Jong, 2007).

Automatic associations can be activated in parallel with explicit cognitions, even when they have a diverging meaning. For instance, an individual with a history of emotional abuse might know on an explicit level that she is not a worthless person when someone is yelling at her. Despite this knowledge, she will automatically feel worthless and may start crying. Automatic processes may thus be of importance in maladaptive affective behavior and are therefore assumed to play an important role in the

development and maintenance of depressive and/or anxiety disorders. However, to our knowledge, no study has yet examined (dysfunctional) automatic self-associations in individuals reporting a history of CA.

Automatic self-associations are often indexed through the use of indirect performance measures (e.g. De Jong, Pasman, Kindt, & van den Hout, 2001). Perhaps the most often used task to assess automatic self-associations is the Implicit Association Test (IAT) (Greenwald, McGhee, & Schwartz, 1998). The IAT is a computerized reaction time task, in which participants are required to sort stimuli according to two contrasted target concepts (e.g. me, other) and two attribute concepts (e.g. depressed, elated). The premise is that when a target and attribute that are strongly associated in memory share the same response key, the participant will be fast on sorting them. Accordingly, it has recently been shown that depressed individuals are faster to categorize '*me*' with depressed words (i.e. showed relatively strong self-depressive associations), anxious individuals are fast to sort '*me*' with anxious words, and patients with comorbid depression and anxiety disorder are fast on both (Glashouwer & de Jong, 2010).

Taken together, the link between CA and depressive and/or anxiety disorders has been well established (e.g. Gibb, Chelminsky, and Zimmerman, 2007), and enhanced automatic self-depressive associations have been found in individuals with a current depression, and enhanced self-anxiety associations in individuals with a current anxiety disorder (Glashouwer and de Jong, 2010). However, until now, it is unknown whether individuals who report CA are also marked by enhanced automatic self-depressive and/or self-anxiety associations, and which type of abuse is most associated with these enhanced automatic self-associations.

The main aim of this study is, therefore, to examine whether individuals reporting a history of CA show stronger automatic self-depression and/or self-anxiety associations than individuals who report no childhood abuse in a large cohort study (Netherlands Study of Depression and Anxiety (NESDA), N = 2981) (Penninx et al., 2008). Moreover, we will examine whether these enhanced negative automatic self-associations are a generic consequence of CA, or whether they are (partly) dependent on the presence of current and/or past depressive and/or anxiety disorders. In line with Rose and Abramson (1992), the third aim of this study is to investigate whether childhood emotional abuse is specifically linked with enhanced automatic self-depression and/or self-anxiety associations. Furthermore, we will investigate whether, in line with findings on explicit self-associations (Gibb, 2001; Liu, Alloy, Abramson, Jacoviello, & Whitehouse, 2009; Wright et al., 2009), enhanced automatic self-depressive or self-anxiety associations mediate the relationship between childhood emotional abuse and depressive, or anxious symptomatology. Finally, to investigate whether CA has a specific or similar association with automatic versus explicit associations, we will examine the impact of CA on explicit ratings of self-depression and self-anxiety.

METHODS

SAMPLE

This study was carried out in the context of the NESDA (Penninx et al., 2008), a multi-center, longitudinal, cohort study, designed to examine the long-term course and consequences of anxiety and depressive disorders. This study concerns the baseline assessment that started in September 2004 and was completed in February 2007. The study protocol was approved centrally by the Ethical Review Board of the VU University Medical Center Amsterdam and subsequently by the local review boards of each participating center. Recruitment of the respondents took place in the general population, in general practices, and in mental health care institutions in order to recruit individuals reflecting various settings and developmental stages of psychopathology.

Inclusion criteria in this study were: age between 18 and 65 years, and a current (during the past month) or past (lifetime) diagnosis of Major Depressive Disorder (MDD), and/or a current or past anxiety disorder (General Anxiety Disorder, Panic Disorder, Social Phobia and/or Agoraphobia). Furthermore, non-clinical controls without a present or past diagnosis were included (Healthy Controls, HC's). Exclusion criteria were a current diagnosis of psychotic disorder, bipolar disorder, or severe addiction disorder and not being fluent in Dutch. In total, 2981 participants (66.5% female; age M = 41.9 years, SD= 13.0) were included. After complete verbal and written description of the study to the participants, written consent was obtained.

DIAGNOSTIC MEASURES

Depressive and anxiety disorders were determined by means of the Composite Interview Diagnostic Instrument (CIDI; WHO version 2.1), which classifies diagnoses according to the DSM-IV criteria (APA, 2001). The CIDI is used worldwide and WHO field research has found high interrater reliability (Wittchen et al., 1991), and high test-retest reliability (Wacker, Battegay, Mullejans, & Schlosser, 2006). Depression severity in the past week was measured with the self-report Inventory of Depressive Symptomatology (IDS; Rush et al., 1986). Severity of anxiety symptomatology of the past seven days was measured with the Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988).

CHILDHOOD ABUSE

CA was assessed through the use of the Nemesis trauma interview (De Graaf, Bijl, ten Have, Beekman, & Vollebergh, 2004a; 2004b). In this interview, respondents were asked whether they had experienced emotional neglect, emotional abuse, physical abuse and/or sexual abuse before they were 16 years of age. Responses to these enquiries were recorded as: never, once, sometimes, regularly, often, or very often.

Emotional neglect was described to participants as follows: 'people at home didn't listen to you, your problems were ignored, you felt unable to find any attention or support from the people in your house'. Emotional abuse was defined as: 'you were cursed, unjustly punished, your brothers and sisters were favored – but no bodily harm was done'. Physical abuse was defined as: 'being kicked, hit with or without an object, or being physically maltreated in any other way'. Sexual abuse was defined as follows: 'being touched sexually by anyone against your will, or being forced to touch anyone sexually, or pressured into sexual contact against your will'.

CA was defined as multiple incidents (>once) of emotional neglect, emotional-, physical- and/or sexual- abuse before the age of 16 years, because (particularly in the case of emotional abuse and/or emotional neglect) we assumed that only multiple incidents of CA may lead to changes in automatic associations over period of years (25 on average). In addition, by excluding individuals who reported a history of CA that had occurred once (n=241), we wanted to construct two very distinct groups (CA vs. No Abuse).

Because emotional abuse rarely occurs in isolation, and often takes place in the context of emotional neglect (of all participants reporting CA in our sample of 3.5% reported emotional abuse without other concurrent types of abuse, and 89% reported emotional abuse and emotional neglect), we combined emotional abuse and emotional neglect to construct a new variable, Childhood Emotional Maltreatment (CEM; emotional abuse and/or emotional neglect that occurred more than once). See also the American Professional Society on the Abuse of Children (APSAC) for a similar definition (Baker, 2009; Bingelli, Hart, & Brassard, 2001; Hart, Germain, & Brassard, 1987). Amongst the individuals reporting CEM, 31% also reported physical abuse, and 29% also reported sexual abuse. In addition, 38% of all individuals reporting sexual abuse also reported physical abuse.

Implicit Association Test (IAT)

To measure automatic self-depression and self-anxiety associations, two IATs were constructed following the design of Egloff and Schmukle (2002). The participants completed the IAT in a fixed order, with the depression IAT first and the IAT anxiety second. The order of the category combinations was fixed across participants in order to enhance the sensitivity of the IAT as a measure of individual differences, which is important in the view of the prospective design of the NESDA (Asendorpf, Banse, & Mucke, 2002; Schnabel, Banse, & Asendorpf, 2006; Steffens & König, 2006). For both IATs the target labels were me and other (Pinter & Greenwald, 2005). The attribute labels were depressed and elated for the depression IAT and anxious and calm for the anxiety IAT. Each category consisted of five stimuli (see supplement). Words from all four concept categories appeared in mixed order in the middle of a computer screen and participants were instructed to sort them with a left (Q) or right (P) response key.

Explicit measures of self-depression and self-anxiety associations were also obtained. Participants rated all attribute stimuli (i.e. depressed, elated, anxiety and calm words, see supplement) that were used in the IATs on a 5-point scale, indicating to what extent the word generally applied to them (1 = hardly/not at all, 5 = very much). The correlation coefficients of the explicit and automatic self-depression and self-anxiety associations are shown in Table 1. For a more detailed description of the procedure, see Glashouwer and de Jong (2010).

Table 1. Correlation Matrix of automatic ratings of self-depressive and self-anxiety associations

Measure	1.	2.	3.
1. IAT anxiety			
2. IAT depression	.49 **		
3. Self-anxiety rating	.37 **	.35 **	
4. Self-depression rating	.31 **	.38 **	.77 **

Note. **=P<.01

We also like to note that in this study we have adapted the descriptors "self-depression" and "self-anxiety" for the IAT depression and the IAT anxiety tests, because these were the terms that were used in the paper of Glashouwer and de Jong (2010), where the same IATs were used in the same sample. The terms self-depression and self-anxiety in this study merely refer to IAT depression and IAT anxiety scores, and not to whether a person associates themselves with being depressed or anxious or having depressive or anxious symptoms, as these kinds of associations are different from the associations that are actually assessed by the present IATs.

IAT scores were computed according to the now widely used algorithm proposed by Greenwald et al. (2003). We report the D4-measure. Duplicating all statistical analyses using the traditional effect measurement (Greenwald et al., 1998) revealed a similar pattern of results as with the D-measure. We decided to report the D-measure so as to comply with other studies using the IAT as an index of automatic associations. Positive IAT effects indicate relatively fast responses when me shared the response key with either anxious or depressed. For descriptive purposes, the mean scores in ms per block per group are summarized in Table 2. The internal consistency of the present IATs was good, with Spearman-Brown corrected correlations between test halves of 0.82 for the depression IAT and 0.87 for the anxiety IAT (test halves were based on trials 1, 2, 5, 6, 9, 10, etc. v. 3, 4, 7, 8, 11, 12, etc.).

To compute the explicit self-associations, the mean ratings of the calm (elated) IAT-stimuli were subtracted from the mean ratings of the anxious (depressed) IAT-stimuli. Hence, a positive effect indicates a strong explicit association between me and anxious (or me and depressed). The internal consistency of the explicit self-associations was good, with Cronbach's α =.94 for the difference scores of anxious and calm words and α =.95 of depressed and elated words.

Of the 2981 participants that were included in the NESDA, 129 had no IAT data, due to technical problems. Furthermore, we excluded ten participants from the analyses because more than 10% of the IAT trials were below 300 ms, suggesting that they were trying to respond too rapidly. In addition, we discarded 5 participants because of unusual IAT scores (>5 SD divergent from mean) that were explained by a very slow overall responding tendency (>4000 ms.) and/or high overall error rates (>28.8%). Consequently data of 2837 participants were available for the analysis.

GROUPS

Following the design of Glashouwer and de Jong (2010), groups were constructed based on current or remitted (R-) major depressive disorder (MDD), anxiety disorder (AD), both MDD &AD, or healthy controls (HC). Individuals with a current or lifetime dysthymia and/or minor depression (without MDD or anxiety disorders) were excluded from the analysis (n=133). Altogether, this resulted in the following groups: individuals reporting a history of CA (i.e. MDD (n=151), AD (n=259), MDD&AD (n=300), R-MDD (n=120), R-AD (n=53), R-MDD&AD (n= 183), and HC (n=133)), and individuals reporting No Abuse (i.e. MDD (n=109), AD (n=214), MDD&AD (n=144), R-MDD (n=172), R-AD (n=74), R-MDD&AD (n=144), and HC (n=457)). Participant characteristics and scores on the depression and anxiety IAT and the

Table 2. Mean and standard errors of demographic, explicit ratings of self-association and automatic self-associations scores of all groups.

	Individuals with a current depressive and/or anxiety disorder					Individuals remitted (R) from a depressive and/or anxiety disorder					Healthy controls	
	MDD Abuse	MDD No Abuse	AD Abuse	AD No Abuse	MDD&AD Abuse	MDD&AD No Abuse	R-MDD Abuse	R-MDD No Abuse	R-AD Abuse	R-AD No Abuse	R-MDD&AD Abuse	R-MDD&AD No Abuse	HC Abuse	HC No Abuse
N	151	109	259	214	300	144	120	172	53	74	183	114	133	457
Female	66.9%	50.5%	71.0%	59.8%	70.3%	54.9%	67.5%	63.9%	79.2%	58.1%	75.4%	70.2%	69.9%	56.9%
Education	11.79	11.54	12.02	12.24	11.13	10.92	12.99	12.66	12.89	12.24	12.20	12.73	12.91	12.68
(SE)	0.27	0.27	0.20	0.22	0.19	0.25	0.32	0.23	0.45	0.37	0.24	0.28	0.29	0.15
Age	42.52	40.39	43.47	40.68	42.59	40.99	44.70	41.40	45.36	38.31	43.07	39.73	46.02	39.36
(SE)	0.99	1.25	0.75	0.90	0.64	1.03	1.12	1.04	1.90	1.79	0.87	1.26	1.12	0.70
self-dep rating	-0.13	-0.45	-0.83	-1.59	0.60	0.26	-2.03	-2.08	-2.04	-2.31	-1.55	-1.74	-2.44	-2.79
(SE)	0.12	0.16	0.09	0.08	0.09	0.12	0.11	0.09	0.15	0.12	0.09	0.11	0.08	0.04
self-anx rating	-0.06	-0.25	0.40	-0.06	1.15	1.07	-1.35	-1.55	-1.22	-1.42	-0.74	-1.06	-1.75	-2.30
(SE)	0.11	0.13	0.08	0.09	0.07	0.11	0.11	0.09	0.16	0.13	0.09	0.12	0.10	0.05
IAT dep	-0.10	-0.11	-0.15	-0.24	-0.03	-0.09	-0.31	-0.33	-0.33	-0.34	-0.18	-0.24	-0.36	-0.41
(SE)	0.03	0.04	0.02	0.02	0.02	0.03	0.03	0.03	0.04	0.04	0.03	0.04	0.03	0.02
IAT anx	-0.21	-0.28	-0.08	-0.16	-0.03	-0.08	-0.46	-0.43	-0.34	-0.44	-0.29	-0.36	-0.47	-0.49
(SE)	0.04	0.05	0.03	0.04	0.03	0.05	0.05	0.03	0.06	0.06	0.03	0.04	0.04	0.02

Note. MDD=Major depressive disorder, AD= Anxiety disorder and HC =Healthy controls, dep=depression, anx=anxiety

explicit ratings of self-depression and self-anxiety associations are presented in Table 2. The CA vs. No Abuse groups differed significantly relative to age ($F(13,2469)=4.55$, $P<.001$), gender ($\chi 2 =39.66$, $df=1$, $P<.001$) and years of education ($F(13,2469)=7.60$, $P<.001$). Overall, the CA group was generally older, had less years of education and consisted of more females when compared to the No Abuse group.

STATISTICAL ANALYSIS

To investigate the main effect of CA on automatic self-depression and self-anxiety associations, and to investigate whether this effect is potentially dependent on current psychopathology, a repeated measures (RM) ANOVA was performed with Group (MDD, AD, MDD&AD, R-MDD, R-AD, R-MDD&AD and HC) and CA (CA vs. No Abuse) as fixed factors, and IAT depression and IAT anxiety scores as dependent variables. To investigate whether the impact of CA on negative self-associations is affected by gender, age or education level, we repeated the analysis while covarying for gender, age and years of education.

To investigate whether CEM is specifically related to enhanced negative automatic self-association, two forced entry (ENTER) regression analyses were run with dummy variables for CEM, physical abuse, and sexual abuse, as predictors and automatic self-depression association or automatic self-anxiety associations as dependent variable.

To further investigate whether enhanced automatic self-depression and automatic self-anxiety associations mediate the association between CEM and depressive or anxious symptomatology, and to investigate whether the results for implicit associations hold when controlling for explicit cognitions, we conducted tests for simple and multiple mediators using 10 000 bootstraps (Preacher & Hayes, 2004; Preacher & Hayes, 2008), with IAT depression and/or IAT anxiety as mediator(s) between CEM and depressive or anxious symptomatology. All analyses were conducted with $\alpha <.05$, and if necessary corrected using the Bonferroni correction.

Finally, all tests were repeated with explicit ratings of the depression and anxiety words as dependent variables, to investigate if we could replicate previous findings of the impact of CA on explicit self-depression and anxiety ratings, and to investigate whether CA has a specific or similar impact on explicit vs. automatic self-associations.

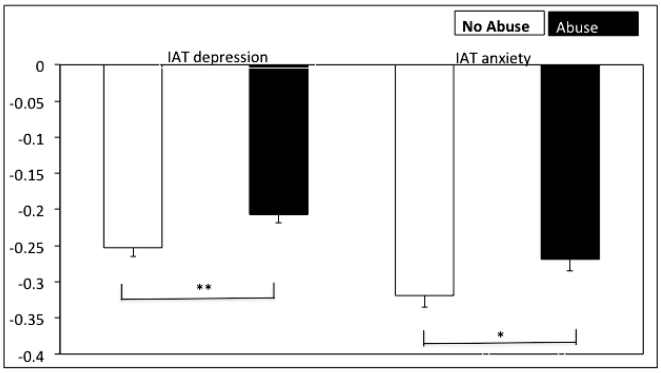
RESULTS

CHILDHOOD ABUSE AND AUTOMATIC SELF- ASSOCIATIONS

In the RM ANOVA, with Group (MDD, AD, MDD&AD, R-MDD, R-AD, R-MDD&AD and HC) and CA (CA vs. non abuse) as fixed factors, and IAT depression and IAT anxiety as dependent variables, CA had a significant main effect on automatic self-depression and self-anxiety associations ($F(1, 2469)=8.34$, $P<.01$, Cohen's $d=.12$). Moreover, there was no interaction between IAT type and CA ($F(1, 2469)=.04$, $P=.69$). These findings suggest

that abused individuals have generally stronger self-depression and self-anxiety associations than non abused individuals. As previously described by Glashouwer and de Jong (2010), group had a significant main effect on automatic self-associations (F(6,2469)=51.82, P<.01, d=.34), and group had a significant interaction with IAT type (F(6,2469)=11.20, P<.001)[I]. In short, depressed individuals had higher automatic self-depression associations; whereas individuals with a current anxiety disorder showed stronger automatic self-anxiety associations, and individuals with a comorbid depressive and anxiety disorder had both high self-depressive and self-anxiety associations (see Glashouwer and de Jong, 2010). No interaction was found between group and CA (F(6,2469)=.50, P=.81), and no interaction was found between group, CA and IAT type (F(6,2469)=.69, P=.66). Finally, IAT type had a significant main effect (F(1,2479)=35.62, P<.001, d=.17), showing that participants scored significantly higher on the IAT depression (M=- .23, SE=.01) when compared to the IAT anxiety, (M=- .29, SE=.01).

Figure 1. Adjusted mean (and SE) of IAT depression and IAT anxiety scores



Note. In the ANOVAs, group (*MDD, AD, MDD&AD, R-MDD, R-AD, R-MDD&AD and HC*) and abuse (*Abuse vs. No Abuse*) were defined as fixed factors and IAT depression or IAT anxiety as dependent factor. An IAT score closer to 0 indicates stronger associations between me and depression/ anxiety words (*=sign at α<.05, **=sign at α<.01, two tailed).

All results remained significant if the covariates age, gender and years of education were added to the model, including the main effect of CA (F(1,2466)=5.98, P<.05, Cohen's d=.10), indicating that the effect of CA on automatic self-depression and self-anxiety associations cannot be explained by differences in age, gender or years of education. In this analysis, age (F(1, 2453)=.29, P=.59), and education level did not have a significant main effect (F(1, 2453)=1.32, P=.25). Gender did have a significant main effect (F(1,2453)=11.14, P<.01), with females (M=-.24, SE=.01) showing higher

[I] *The effects of depression and anxiety diagnosis (current, past and no history) on implicit and explicit self-depression and self-anxiety associations have been described in detail by Glashouwer and the Jong (2010). Therefore in this paper, these results will not be described in detail.*

negative automatic self-associations than males (M=-.30, SE=.02). However, gender did not interact with CA (F(1, 2453)=.008, P=.93) confirming that gender does not moderate the effect of CA on negative automatic self-associations.

Additionally, in a model where severity of depressive and anxiety symptoms were added as covariates (and group was removed as fixed factor), the main effect of CA remained significant (F(1,2479)=8.37, P<.01, d=.12). Therefore, more severe depressive and/or anxiety symptomatology amongst abused individuals cannot explain the effect of CA on automatic self-depression and self-anxiety associations.

TYPE OF CA AND ENHANCED AUTOMATIC SELF-ASSOCIATIONS

To investigate whether CEM is more related to enhanced negative self-associations, two forced entry (ENTER) regression analyses were run with dummy variables for CEM, physical abuse, and sexual abuse as predictors, and automatic self-depression and self-anxiety associations as dependent variable. The analysis showed that CEM was the strongest predictor of automatic self-depression associations (Beta=.14, t=6.27, P<.001).

The contribution of sexual abuse was marginally significant (Beta=.04, t=1.68, P=.09), and physical abuse did not contribute significantly to automatic self-depression associations (Beta=.00, t=-.15, P=.88). Similarly, in the regression analysis with automatic self-anxiety associations as dependent variable, CEM (Beta=.08, t=3.62, P<.001), sexual abuse (Beta=.06, t=2.61, P<.01) and physical abuse (Beta=.05, t=2.30, P<.05) were all significant predictors of automatic self-anxiety associations, with CEM being the strongest predictor.

Previous studies have suggested that negative self-associations are most likely to develop when the negative self-concepts are explicitly handed to the child (see Rose and Abramson, 1992). Therefore, we specifically wanted to investigate whether emotional abuse in itself is associated with changes in the IAT, outside the context of emotional neglect, and of physical and sexual abuse, leaving only 42 participants with emotional abuse. We performed a RM ANOVA with individuals reporting only emotional abuse (emotional abuse vs. no abuse) and Group (MDD, AD, MDD&AD, R-MDD, R-AD, R-MDD&AD and HC) as fixed factors, and IAT depression and IAT anxiety as dependent variables. Despite the relatively small sample, emotional abuse had a significant main effect on IAT depression and IAT anxiety scores (F(1,1312)=6.19, P<.05, d=.39). A similar analysis with individuals reporting only neglect and no other types of CA (i.e., no emotional abuse, and no physical or sexual abuse, n=306), showed that emotional neglect had a marginal significant main effect on IAT depression and IAT anxiety score (F(1,1576)=3.60, P=.06, d=.23), suggesting that both emotional abuse and emotional neglect are related to enhanced automatic negative self-associations.

MEDIATION ANALYSES.

To further investigate whether enhanced automatic self-depressive associations mediate the association between self-reported CEM (CEM n=1105, No Abuse n=1284) and depressive or anxious symptomatology, we performed a test for simple mediation (Preacher & Hayes, 2004) using 10 000 bootstraps, with CEM as independent factor, IAT depression or IAT anxiety as mediator, and IDS or BAI score as dependent variables. In this model, CEM was significantly related to depressive symptomatology (see Table 3 for the pathway coefficients). When IAT depression was added as a mediator, the relation between CEM and depressive symptomatology partially reduced, and this reduction was significant (Z=7.15, P<.001). In a second mediation analysis, CEM was significantly related to anxious symptomatology, and when IAT anxiety was added as a mediator, this association reduced significantly, but not entirely (Z=5.99, P<.001). In addition, multiple mediator analyses (Preacher & Hayes, 2008) revealed that when explicit self-depressive, or self-anxiety associations were added as mediators in the model, automatic self-depressive associations and automatic self-anxiety associations remained significant mediators of the relationship between CEM and depressive or anxious symptomatology (Table 3). These findings not only suggest that negative automatic self-depressive or self-anxiety associations partially mediate the relationship between CEM and depressive or anxious symptomatology, these findings also suggest that automatic and explicit self-associations are differentially related to depressive and anxious symptomatology.

CHILDHOOD ABUSE AND EXPLICIT RATINGS OF SELF-ASSOCIATIONS

Using a similar RM ANOVA as with the IAT, CA had a main effect on ratings of self-depression and self-anxiety associations

Table 3. Negative self-associations mediate the relation between CEM and depressive or anxious severity.

			Pathways coefficients (ß)					*Bootstrap results IV→MV→DV*		
IV	MV	DV	IV→MV	MV→DV	IV→DV	IV→MV→DV	Effect	Z score	Effect	SE
CEM	IAT depression	IDS	0.13 ***	10.73 ***	9.85 ***	8.48 ***	1.36	7.15 ***	1.36	0.19
CEM	IAT anxiety	BAI	0.14 ***	6.03 ***	5.52 ***	4.69 ***	0.82	5.99 ***	0.82	0.14
CEM	Explicit depression	IDS	1.05 ***	6.06 ***	9.85 ***	3.46 ***	6.39	15.15 ***	6.39	0.42
CEM	Explicit anxiety	BAI	1.04 ***	4.16 ***	5.52 ***	1.20 ***	4.32	14.56 ***	4.32	0.30
CEM	IAT depression	IDS	0.13 ***	1.89 ***	9.85 ***	3.39 ***	0.24	3.23 **	0.24	0.07
	Explicit depression		1.05 ***	5.89 ***			6.23	15.02 ***	6.22	0.41
CEM	IAT anxiety	BAI	0.14 ***	1.44 ***	5.52 ***	1.17 ***	0.20	3.56 ***	0.20	0.06
	Explicit anxiety		1.04 ***	4.00 ***			4.15	14.37 ***	4.15	0.30

Note. CEM: *n* =1105, No Abuse: *n* =1284, IV=independent variable, MV= mediator variable, DV= dependent variable, IDS= Inventory of Depressive score, BAI= Beck Anxiety Inventory score, ***=sign at α<.001, **=sign at α<.01, two tailed

(F(1,2469)=45.43, P<.0001, d=.27). There was no interaction between CA and ratings of self-anxiety or self-depressive associations (F(1,2469)=.58, P=.45), indicating that the CA group had higher ratings of both self-depressive and self-anxiety associations. The main effect of CA remained significant if the covariates age, gender and years of education were added to the model (F(1,2466)=40.70, P<.000, d=.26). In addition, in a model where severity of depressive and anxiety symptoms were defined as covariates (and group was removed as fixed factor), the main effects of CA also remained significant (F(1,2479)=30.23, P<.01, d=.22).

TYPE OF CA AND ENHANCED EXPLICIT SELF-ASSOCIATIONS

Two forced entry (ENTER) regression analyses were run with dummy variables for CEM, physical abuse, and sexual abuse as predictors, and explicit self-depression, or self-anxiety associations as dependent variable. In line with findings on the automatic self-associations, CEM was the strongest predictor of self-depression (Beta=.28, t=12.87, P<.001), and self-anxiety associations (Beta=.26, t=11.87, P<.001). Physical abuse was a significant predictor of both self-depression associations (Beta=.05, t=2.45, P<.01) and self-anxiety associations (Beta=.06, t=2.80, P<.001), and sexual abuse predicted self-anxiety associations (Beta=.04, t=2.08, P<.05), but not self-depression associations (Beta=.02, t=.96, P=.34).

In addition, a test for simple mediation (preacher and Hayes, 2004) using 10 000 bootstraps, with CEM (CEM n=1105, No Abuse n=1284) as independent, explicit self-depression or explicit self-anxiety associations as mediator, and IDS or BAI score as dependent variable, showed that negative explicit self-depressive or self-anxiety associations partially mediate the relationship between CEM and depressive or anxious symptomatology (see Table 3).

DISCUSSION

The first aim of this study was to investigate whether childhood abuse (CA) was associated with enhanced automatic negative self-depression and self-anxiety associations. In line with our predictions, CA was associated with both increased automatic self-depression and self-anxiety associations. Similarly, and in line with previous studies (Alloy et al., 2006; Gibb, 2002; Gibb et al., 2003; Gibb & Abela, 2008; Wright et al., 2009), CA was also associated with enhanced explicit self-depressive and self-anxiety associations. The effects of CA remained significant when adding severity of depressive and anxiety symptomatology as covariates to the model, suggesting that these effects cannot be explained by more severe depression and/or anxiety symptoms amongst individuals reporting CA. Moreover, the relationship between CA and negative self-associations was consistently found within all groups (i.e., current, past, or no history of depressive and/or anxiety disorders). This pattern indicates that the stronger negative self-associations in individuals with a history of CA cannot beinterpreted as mere

symptoms of concurrent psychopathology. However, given the prominent role that is attributed to negative self-associations in mood and anxiety disorders (e.g. Beck, 2008), it seems reasonable to assume that these enhanced negative self-associations increase an individual's generic vulnerability to develop a mood and/or anxiety disorder. In the face of other factors, such as genetic make-up, stressful life events and/or (lack of) social support, this generic vulnerability may lead to the development of psychopathology (see Beck, 2008; Caspi et al., 2003; Caspi & Moffitt, 2006).

In line with our hypothesis, CEM (consisting of emotional neglect and psychological abuse) was the most potent predictor of both automatic self-depression and automatic self-anxiety associations. In addition, sexual and physical abuse were only significant predictors of automatic self-anxiety associations. Similarly, ratings of self-depression and self-anxiety associations were also especially enhanced in individuals reporting a history of CEM. Additionally, subsequent analyses revealed that relatively small subgroups of individuals reporting emotional abuse (n=42), and even emotional neglect (n=306), also showed significantly enhanced automatic negative self-associations. Moreover, in these groups the effect sizes for the automatic (d=.39 and .23) were larger than those for the total CA group (d=.12), suggesting that a history of emotional abuse and emotional neglect is sufficient to enhance negative automatic self-associations.

Taken together, our findings suggest that CEM is related to both enhanced deliberate and automatic self-associations. These findings are in line with earlier findings of a strong relationship between emotional abuse and explicit negative self-associations (Alloy et al., 2006; Gibb, 2001; Gibb, 2002; Gibb et al., 2003; Gibb & Abela, 2008; Wright et al., 2009).

In addition, our findings build on and extend the hypothesis that compared to childhood physical and sexual abuse, emotional abuse is more likely to enhance negative self-cognitions (see Rose & Abrahamson, 1992). Moreover, our findings also suggest that negative self-associations do not only develop when these are explicitly handed to the child during emotionally abusive episodes (e.g. '*you are such a stupid child*'), but also seem to arise in the context of emotional neglect, where the meaning is mostly suggested, rather than explicitly stated (e.g. '*I am such a worthless child, because mommy doesn't give me any attention*').

Moreover, the mediation analyses revealed that automatic (and explicit) negative self-associations statistically partially mediate the relation between CEM and depression or anxiety severity. Perhaps even more importantly, tests of multiple mediators (Preacher & Hayes, 2008) revealed that, when explicit self-associations were also added as a mediator in the model, automatic self-associations remained significant mediators of the relationship between CEM and depressive or anxious symptomatology. These results suggest that both automatic and explicit self-associations might (partly) have an independent contribution to the development of depressive or anxious symptomatology. Together with our findings that CEM is related to enhanced negative self-associations irrespective of current

psychopathology, these findings indicate that CEM is related to depressive and anxious symptomatology, although CEM in itself does not predict whether someone actually develops a depressive or anxiety disorder. Rather, and in line with Beck (2008), experiencing CEM might be marked as a generic cognitive vulnerability factor for the development of (more severe) depressive and anxiety symptoms via the generation of negative automatic self-associations.

It should be acknowledged that the cross sectional design of our study does not allow any firm conclusion regarding the direction of the present relationship between CEM and enhanced negative self-associations, nor between negative self-associations and depression. Thus the present findings should be interpreted with care. To arrive at more solid grounds in this respect it would be important to test further the proposed interrelationship in a longitudinal design. As a next step it might therefore be helpful to investigate whether CEM-related negative automatic (and explicit) self-depression and self-anxiety associations indeed have prognostic value for the onset of mood and/or anxiety disorders in a prospective design (e.g. Gibb et al., 2001; Liu et al., 2009; Wright et al., 2009).

Although the differences between the abused and non-abused individuals regarding automatic and deliberate self-associations were generally in the same direction, the correlations between the implicit and explicit measurements were only moderate (see Table 1). This is consistent with other studies (e.g. Hofmann, Gawronski, Gschwendner, Le, & Schmitt, 2005) and in accordance with the assumption that different memory processes form the basis of explicit and automatic cognitions (Gawronski & Bodenhausen, 2006).

The effect sizes of CA on explicit negative self-associations appeared larger (i.e. d ranging between .22 -.45) than those of the automatic self-associations (i.e. d ranging between .10 and .12), even though it should be noted that in the subsamples of individuals reporting only emotional abuse or only emotional neglect, the effect sizes for the automatic self-associations (d=.39 & d=.23) were similar when compared to the effect sizes found on the explicit measures (i.e. d=.22-.45), suggesting that emotional abuse and emotional neglect have a similar impact on both automatic and explicit negative self-associations. Nevertheless, at least for CA in general this seems to suggest that abuse in childhood mostly influences deliberate associations rather than automatic self-associations and are therefore more informative when studying the impact of negative self-associations on maladaptive emotional behavior. In addition, the mediation analyses suggest that when compared to automatic self-associations, explicit self-associations are stronger mediators of the relationship between CEM and depressive or anxious symptomatology. However, the difference in magnitude should be interpreted with care, because shared method variance between the explicit ratings and (self-reported) CA may have artificially inflated their

relationship compared to the relationship between CA and automatic associations. Moreover, the explicit measure in this study consisted of ratings of to what extent the participants considered that the stimulus words applied to them, and is not an empirically tested measure, although the internal consistency was good (Cronbach's Alpha's ranging from .94 to .95). To further examine the differential importance of explicit and automatic self-associations, it would be important to test the predictive validity of automatic and explicit self-associations for the onset or recurrence of anxiety and depressive episodes in prospective studies (e.g., Huijding & de Jong, 2009; Engelhard, Huijding, van den Hout & de Jong, 2007).

A main effect of IAT type was observed, indicating that participants scored significantly higher on the IAT depression when compared to the IAT anxiety. However, it is difficult to interpret such a direct comparison between the associations of CA with automatic self-depression versus automatic self-anxiety associations, because the depression IAT was always presented before the anxiety IAT, and IAT effects tend to decrease with the number of IATs presented to a participant. In the context of NESDA we nevertheless preferred a fixed order to optimize the sensitivity of the IAT as a measurement of individual differences (Asendorpf et al., 2002; Schnabel et al., 2006; Steffens & König, 2006; Glashouwer & De Jong, 2010). Additionally, the two IATs did not match up conceptually. That is, the attribute words of the IAT depression tend to be more about self-worth (i.e., useless, inadequate), whereas the IAT anxiety tended to focus more on symptoms of the disorder (i.e., anxious, afraid). In sum, differences between the two IATs might be due to several factors, including conceptual differences, which hamper a straightforward interpretation.

The cross-sectional design of our study limits our inferences regarding the causality of our findings. The assessment of CA was based on retrospective self-report, and may therefore be susceptible to distortion and/or inflation. It could be argued that individuals with enhanced negative self-associations might be more prone to over report histories of CA. However, our findings of enhanced explicit negative self-associations in individuals reporting CEM are in line with a number of prospective studies that show that children exposed to emotional maltreatment subsequently develop negative cognitive schemas (e.g. Gibb, 2001), and that cognitive schemas are predictive of depressive symptomatology in emotionally maltreated individuals over time (Gibb, 2001; Liu et al., 2009; Wright et al., 2009). Our findings, together with these prospective studies, seem to suggest that CEM leads to the development of negative explicit and implicit self-associations, which might constitute a vulnerability factor for the development of depressive and anxiety disorders over time.

Conclusion

To our knowledge, this is the first study showing that CA is related to increased automatic negative self-associations in adulthood. Moreover, due to its transdiagnostic design, this study was able to show that CA is linked

with enhanced negative automatic self-associations, irrespective of whether or not the individual has a current and/or past depression and/or anxiety disorder. Finally, due to the large set of participants (n=2483), and the fact that all types of CA (CEM, physical- and sexual- abuse) were measured, we were able to show that CEM has the strongest link with enhanced (automatic and explicit) negative self-associations. Taken together, our results are consistent with the notion that CEM plays a crucial role in increasing one's negative self-associations. Our findings build to the increasing understanding of the prolonged and adverse impact of CEM (see Gilbert et al., 2009). Nevertheless, within the scientific and public domain, the effects of CEM still seem to be considerably underestimated (Gilbert et al., 2009). Informing parents, teachers, general practitioners and therapists about the possible detrimental impact of CEM, may help to reduce this underestimation. Subsequently, this might lead to better attention to and perhaps even a reduction in the occurrence of CEM and may eventually improve the treatment of individuals reporting CEM. Consequently, informing society may thus lead to a reduction in (the shaping of) dysfunctional self-associations in individuals reporting a history of emotional maltreatment.

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SUPPLEMENT

IAT STIMULUS WORDS

Me: I, myself, self, my, own
Other: other, you, they, them, themselves
Anxious: anxious, afraid, nervous, insecure, worried
Calm: calm, balanced, placid, secure, relaxed
Depressed: useless, pessimistic, inadequate, negative, meaningless
Elated: positive, optimistic, active, valuable, cheerful
Note. Words are translated from Dutch

Chapter 3: Intrusions of autobiographical memories in individuals reporting childhood emotional maltreatment

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ABSTRACT

During childhood emotional maltreatment (CEM) negative attitudes are provided to the child (e.g; ''*you are worthless*''). These negative attitudes may result in emotion inhibition strategies in order to avoid thinking of memories of CEM, such as thought suppression. However, thought suppression may paradoxically enhance occurrences (i.e. intrusions) of these memories, which may occur immediately or some time after active suppression of these memories. Until now, studies that examined suppressive coping styles in individuals reporting CEM have utilized self-report questionnaires. Therefore, it is unclear what the consequences will be of emotion inhibition styles on the intrusion of autobiographical memories in individuals reporting CEM. Using a thought suppression task, this study aimed to investigate the experience of intrusions during suppression of, and when no longer instructed to actively suppress, positive and negative autobiographical memories in individuals reporting Low, Moderate and Severe CEM compared to No Abuse (total N=83). We found no group differences during active suppression of negative and positive autobiographical memories. However, when individuals reporting Severe CEM were no longer instructed to suppress thinking about the memory, individuals reporting No Abuse, Low CEM, or Moderate CEM reported fewer intrusions of both positive and negative autobiographical memories than individuals reporting severe CEM. Finally, we found that intrusions of negative memories are strongly related to psychiatric distress. The present study results provide initial insights into the cognitive mechanisms that may underlie the consequences of childhood emotional maltreatment, suggesting avenues for successful interventions.

INTRODUCTION

Childhood Emotional Maltreatment (CEM) consists of behavior by a caregiver that conveys to a child that he or she is worthless, flawed, unloved, unwanted, endangered, or valued only in meeting another's needs (APSAC, 1995; Baker, 2009; Gilbert, Widom, Browne, Fergusson, Webb, Janson, 2009). Besides emotional abuse (e.g. yelling at, or cursing the child), CEM also comprises emotional neglect (e.g. ignoring the child, favoring other siblings, not giving support or attention to the child). As such, experiences of CEM strengthen the development of negative cognitive (self-) schemas in these children about the self and significant others (see Beck, 2008; Rohner, 2004; Rose & Abramson, 1992). This is corroborated by an accumulating number of studies indicating that CEM is strongly related to negative dysfunctional self-attitudes and negative (self-) inferential styles (Alloy, Abramson, Smith, Gibb, & Neeren, 2006; Gibb, 2002). These negative cognitive schemas can persist into adulthood, that is, more than 20 years after the maltreatment took place (van Harmelen, et al., 2010). As a result, emotionally maltreated individuals are more vulnerable to develop and/or maintain a mood and/or anxiety disorder in adulthood (Beck, 2008; Rohner, 2008; Spinhoven et al., 2010). This is supported by findings showing that negative self-inferential styles mediated depressive and anxious symptomatology in individuals reporting CEM (Gibb, Wheeler, Alloy, & Abramson, 2001; van Harmelen, et al., 2010; Wright, Crawford, & Del Castillo, 2009)

In response to memories and experiences of childhood maltreatment, emotionally abused individuals may try to avoid thinking about these distressing thoughts or memories. Subsequently, over the course of years, this habitual coping style may translate into the avoidance of negative memories in general, and may even apply to memories that are unrelated to the maltreatment. 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 in general (Krause, Mendelson, & Lynch, 2003). Because of its reliance on mental control, successful suppression of distressing content has been associated with high intelligence, strong working memory capacity, and is inversely related to presence of psychopathology (Brewin & Beaton, 2002; Dalgleish, Yiend, Schweizer, & Dunn, 2009; Dunn, Billotti, Murphy, & Dalgleish, 2009; Geraerts & McNally, 2008). However, attempts to suppress a certain memory or thought may subsequently lead to a preoccupation and an increase in the occurrence of that memory or thought, which is most apt to occur when mental control is relinquished and the individual is no longer trying to suppress the memory or thought (i.e., post-suppression rebound effect) (Wegner, Schneider, Carter, & White, 1987; Wenzlaff & Wegner, 2000). Thus, despite this seemingly useful coping strategy, an enhancement of intrusions of distressing material may occur immediately, or some time after active suppression (i.e. post-suppressive rebound), and is especially prominent in

individuals with an avoidant coping style (Geraerts & McNally, 2008; Wenzlaff & Wegner, 2000).

Intrusions of distressing memories have been found to induce the same mood state and physiological responses that are associated with that memory (Wenzlaff & Wegner, 2000). Furthermore, intrusions of negative material induce heightened accessibility to other negative autobiographical memories that may be more general (Dalgleish & Yiend, 2006), or less specific (Geraerts, Hauer & Wessel, 2010). In this way, intrusions of negative autobiographical memories may activate and strengthen individuals' negative cognitive self-schemas (Beck, 2008), thereby increasing individuals' vulnerability to the development of depressive disorders. In line with these findings, 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 mediate 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 (Krause, et al., 2003; Reddy, et al., 2006; Rosenthal, et al., 2006). However, self-report questionnaires are prone to inflation and distortion related to individual's psychiatric distress (McNally, 2003). Therefore, it is unclear what the consequences will be of emotion inhibition on the intrusion of autobiographical memories in individuals reporting CEM. It is possible that individuals reporting CEM might report fewer intrusions during active suppression, as they are more adept at suppressing these memories (e.g. Geraerts, Merckelbach, Jelicic, & Habets, 2007). In addition, thought suppression may also result in the experience of more intrusions when individuals reporting CEM no longer actively suppress thinking about these autobiographical memories. Finally, it is unknown whether (possibly) enhanced intrusions in individuals reporting CEM are specific to negative autobiographical memories (e.g. McNally & Ricciardi, 1996), or whether they generalize to positive autobiographical memories.

This study aimed to investigate the impact of varying degrees of CEM on intrusions during suppression and when no longer instructed to actively suppress positive and negative autobiographical memories. To investigate suppression and post-suppressive rebound of autobiographical memories in individuals reporting varying degrees of CEM or No abuse, we utilized a thought suppression task. We hypothesized that level of CEM is associated with 1) reduced intrusions during the suppression phase, and 2) increased intrusions of negative autobiographical memories when suppression is relinquished when compared to individuals that report no history of childhood abuse. Furthermore, given the function of the avoidance strategy, we merely expect this to occur in the context of negative memories; we do not expect differences between individuals reporting CEM or no abuse in

childhood with respect to positive emotional memories. Finally, we will explore whether intrusions (during, or post-, suppression) during the thought suppression task are related to explicit measurements (self-report questionnaires) of avoidance strategies, and/or general distress.

METHOD

PARTICIPANTS

The sample consisted of 83 first year psychology students, 27 males and 56 females, with a mean age of 19.7 $\pm$ 1.93 years (see Table 1 for additional demographics). Participants received course credits for participating in this study. All participants provided written informed consent.

CHILDHOOD TRAUMA

History of childhood maltreatment was assessed with the Dutch version of the Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998; Bernstein, et al., 1994); the Jeugd Trauma Vragenlijst (JTV; Arntz & Wessel, 1996). In the CTQ, a total of 28 items are scored on a 5-point scale, ranging from 1=never true to 5=very often true. The CTQ retrospectively measures five subtypes of childhood abuse: emotional abuse, sexual abuse, physical abuse, emotional neglect and physical neglect. The CTQ is a sensitive and reliable screening questionnaire with Cronbach's alpha for the CTQ subscales varying between .63-.91 (Thombs, Bernstein, Lobbestael, & Arntz, 2009).

Emotional maltreatment in childhood was defined as a history of emotional neglect and/or emotional abuse before the age of 16 years according to the CTQ, see the American Professional Society on the Abuse of Children (APSAC) for a similar definition (APSAC, 1995; Baker, 2009; Glaser, 2002). In our study, Cronbachs alpha for the emotional abuse subscale was .85, for the emotional neglect subscale .86, and for the combined emotional abuse and neglect scales was .89. Overall CEM score was defined as the highest score on the emotional abuse or emotional neglect subscale of the CTQ (e.g. if emotional abuse score was 14, and emotional neglect score was 12, overall CEM score is 14). In the current sample, CEM scores ranged from 5 to 23; Median = 10.

Because we were specifically interested in the impact of emotional maltreatment, we excluded individuals reporting moderate to severe physical or sexual abuse (i.e. a CTQ score of >7 for sexual abuse, and >9 for physical abuse, based on Bernstein & Fink, 1998). This resulted in the exclusion of one participant who reported severe sexual abuse (i.e. sexual abuse subscale score = 16).

Finally, groups were formed based on the 25th, 50th, and 75th percentiles of overall CEM score (i.e. 7, 10 and 14). The final sample consisted of the following four groups; No Abuse (i.e. CEM score 5-7; n=24), Low CEM (i.e. CEM score 8-10; n=22), Moderate CEM (i.e. CEM score 11-14; n=20) and Severe CEM (i.e. CEM score> 14; n=16)(see Table 1).

PSYCHOPATHOLOGY

In order to assess general distress, we utilized the Dutch version of the Symptom Check-List 90 Revised (SCL-90R; Arrindell & Ettema, 2003; Derogatis, 1983). The SCL-90 is a self-report questionnaire designed to assess major symptoms of psychic distress and the experience of psychopathology, represented in nine primary symptom dimensions (Arrindell & Ettema, 2003). The Dutch version of the SCL-90-R consists of 90 items concerning a patient's symptom distress, each item rated on a five-point Likert scale (1–5) varying from 'not at all' to 'extremely'. These items combined form a total score that is indicative of psychiatric functioning in general. In terms of psychometric properties, the internal consistency reliabilities for the nine dimensions of the SCL-90-R range from .77 to .90. Test-retest reliability for the SCL-90-R ranges between .80 and .90 (Derogatis & Savitz, 2000).

Table 1. Mean (M) and Standard Deviations (SD) of demographics and clinical characteristics per CEM group.

Groups		**No Abuse (*n* =24)**		**Low CEM (*n* =22)**		**Moderate CEM (*n* =21)**		**Severe CEM (*n* =16)**		X^2	P
Gender	*n* Female/Male	18/6		12/10		14/7		12/4		2.71	0.43
		M	SD	M	SD	M	SD	M	SD	F	P
Age		19.79	2.09	19.59	1.47	19.57	1.66	20.06	2.62	0.24	.86
Impact of Event Scale	Total score	9.83	12.89	18.57	17.19	14.76	12.17	22.50	17.93	2.56	.06 #
	Intrusion	5.29	6.66	9.18	8.66	7.38	6.30	8.25	6.98	1.20	.32
	Avoidance	4.54	6.98	8.95	9.12	7.38	7.37	14.25	12.40	3.92	.01 *
SCL-90	Total score	124.00	29.47	125.55	25.13	128.67	28.76	129.31	21.28	0.18	.99
Negative Experience	Frequency	1.58	1.10	2.00	1.72	1.65	1.18	1.63	1.02	0.48	.70
	Negativeness	7.29	1.97	7.52	1.87	7.25	1.77	7.63	1.50	0.18	.91
	Vividness	8.58	1.02	7.59	2.17	7.15	2.16	7.94	1.95	2.35	.08 #
	Stressfulness	5.75	1.94	4.91	2.86	6.05	2.91	6.88	1.36	2.17	.10
	Frightfulness	3.71	2.37	4.91	2.89	5.05	2.96	4.81	2.32	1.22	.31
Positive Experience	Frequency	2.00	1.18	2.50	0.74	2.10	1.07	1.88	1.15	1.37	.26
	Negativeness	1.83	1.17	1.73	0.88	1.85	0.99	2.31	1.85	0.78	.51
	Vividness	7.38	1.64	7.64	2.11	7.45	2.21	8.00	1.71	0.38	.77
	Stressfulness	2.00	2.15	2.32	1.55	2.35	2.21	2.88	2.16	0.60	.62
	Frightfulness	1.79	1.79	1.73	1.42	1.80	1.88	1.94	1.83	0.94	.43

Note . # = P<.10, * = P< .05

IMPACT OF EVENT SCALE (IES).

To assess individuals stress reactions related to a traumatic event, we administered the Impact of Event Scale (IES; Horowitz, Wilner, & Alverez, 1997). The IES assesses individual's most negative life experience. Participants are required to provide a short description of this life event, and to complete a short questionnaire regarding the impact of that event. This questionnaire consists of two subscales, Intrusions, and Avoidance that together measure stress reactions after a traumatic event (Sundin & Horowitz (2002). The reliability of the IES is good, with Cronbach's alpha's ranging from .85 to .95 for the Intrusion subscale, from .77 to .91 for the Avoidance subscale, and from .87 to .96 for the total score (van der Ploeg, Mooren, Kleber, van der Velden, & Brom, 2004). Furthermore, the sub-scales are relatively independent suggesting adequate content validity (van der Ploeg, et al., 2004).

THOUGHT SUPPRESSION TASK

The thought suppression task consisted of two stages, during which participants were instructed to retrieve either a positive or a negative autobiographical memory respectively. The order of the positive and negative autobiographical memory was counterbalanced, so half of the participants started with retrieving a positive autobiographical memory and the other half started with a negative autobiographical memory. Each stage consisted of an imagining period, a suppression period and an expression period, each lasting three minutes.

In the first phase, the imagining period, participants had to select and describe the most positive (or negative) event they had experienced in the past two years. This was called the target experience, and could be either a negative experience (e.g. a fight, a break-up or a bad critique) or a positive experience (e.g. receiving a compliment, engaging in a relationship or celebrating with friends). Participants rated their own target experience on the following four scales: negativeness, vividness, stressfulness, and frightfulness, on a 10 point scale ranging from, for instance, 'very much negative' to 'very much positive'.

In the second phase, the suppression phase, participants were asked to look at the screen of the computer, which was black with a yellow fixation cross in the middle. Participants were instructed to try to suppress any thoughts about the target experience. If they did think about the target experience, they were asked to press a button on the response box.

The third phase, the expression period, was similar to the suppression phase, only now participants were allowed to think about anything they wanted, including the target experience. Participants were again asked to press a button on the response box if they were thinking about the target experience. After this expression phase, participants completed an easy mathematical filler task for three minutes to provide a distraction before moving on to the next phase. After the filler task the first three phases were

repeated with a different autobiographical memory; if the first memory was positive, then the second memory was negative and vice versa.

PROCEDURE

Upon arrival in the lab, participants were informed about the procedure, and completed a written informed consent form. Thereafter, participants conducted the computerized thought suppression task sitting behind a desk on which a PC was situated at a distance of 50 centimeter from the participants. After completing the computerized task, participants completed the SCL-90, the IES and the CTQ respectively. Afterwards, all participants were fully debriefed.

STATISTICAL ANALYSES

All analyses were performed using SPSS version 17. The positive and negative autobiographical events were classified by three independent raters, who were blind to the participant's history of childhood maltreatment. The first independent rater constructed general classifications for the type of memories, which were based on the relationship with a significant other (or self) (self, partner, friends, parents, strangers, external factors), and the type of emotion or experience (pride, compliment, rejection etc) (see Table 2 for the exact classifications used). Thereafter, two other raters independently classified the memories (the classification was exclusive, i.e. all memories were classified as one type of event). Correlations for these two independent raters were r=.86 for the positive and r=.72 for the negative autobiographical memory. Thereafter the raters discussed and categorized all remaining memories that were rated differently in the first phase, resulting in full agreement on all memories.

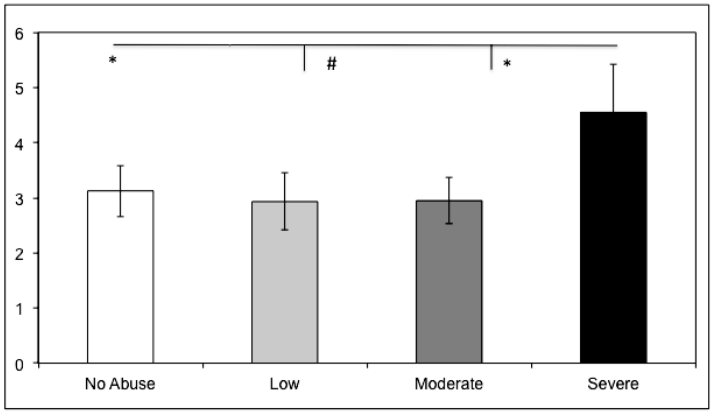
Ratings of the positive and negative autobiographical memory on the scales of negativeness, vividness, stressfulness, and frightfulness were compared using one-way analysis of variance (ANOVA). To determine the impact of CEM on the amount of intrusions of negative or positive autobiographical memories, we performed a Valence (positive, negative)×Phase (suppression- expression) repeated measures (RM) Analysis of Variance (ANOVA), with Group (No Abuse, Low-, Moderate-, Severe CEM) as fixed factor. Per phase and valence type (i.e. negative suppression, negative expression, positive suppression and positive expression), intrusion scores were standardized in order to control for outliers: scores that exceeded Z=3.29 were transformed to 2 times standard deviation above or below the mean (for each individual). For the final analysis, two outlier scores were detected and transformed. Least square difference correction was applied to control for multiple testing. All analyses were conducted with a two-tailed α of $<.05$

Results

Groups

There was no significant difference between the groups in gender (χ^2=2.74 (3) P=.43), age (F(3,79)=.24, P=.86), nor SCL-90 total score (F(3,79)=.18, P=.99) see Table 1. Groups did differ marginally on the Impact of events (IES) total scale score (F(3,79)=2.56, P=.06) with the Low CEM, Moderate CEM and Severe CEM groups having higher IES scores than the No Abuse group (Table 1). Furthermore, groups differed significantly on the IES Avoidance subscale (F(1,79)3.92, P<.05). In the Severe CEM group, individuals reported more Avoidance compared to the No Abuse group, P<.001, the Moderate CEM group, Mean Difference= 6.87, P<.05, and marginally more than the Low CEM group, Mean Difference = 5.29, P=.07, see Figure 1. No other group differences were found on IES avoidance (all Mean Difference's<4.41, P's>.10) nor on the IES Intrusions scale (F(1,79)=1.20, P=.32).

Figure 1. Mean and standard error of IES avoidance level per CEM group.



Note. * = P < .05, # = P < .10.

Selection of Autobiographical events

The types of memories that participants reported in the thought suppression task are depicted in Table 2. For the positive autobiographical memory, all groups most often reported an event in which they felt proud, or relieved due to their own achievement. For the negative memory, the most frequently reported memory in the No Abuse, Low CEM, and Moderate CEM groups concerned the ending of the participant's relationship, or major troubles in their relationship (i.e. 29.2 %, 27.3 %, and 38.1 % respectively). Interestingly, the most often reported negative memory in the Severe CEM group (30%) concerned their parents not showing support or appreciation. This is in contrast with the other groups: In the No Abuse group only 12.5 % of cases reported a memory that involved lack of parental support or appreciation, and in the low and Moderate CEM groups this was reported in

Table 2. Classifications of the pcsitive and negative autobiographical memories.

Groups	No Abuse (*n*=24)	%	Low CEM (*n*=22)	%	Moderate CEM (*n*=21)	%	Severe CEM (*n*=16)	%
Positive memory								
Self, pride and relief in own achievement	13	54.2	14	63.6	9	42.9	7	43.8
Partner, beginning of relationship, or happy moment with p	4	16.7	0		2	9.5	4	25
Friends give compliments, appreciation	1	4.2	0		2	9.5	1	6.3
Friends show support	3	12.5	2	9.1	2	9.5	1	6.3
Parents show support/ appreciat on	1	4.2	0		0		0	
Compliment, appreciation from stranger	2	8.3	1	4.5	2	9.5	0	
Special occasion, party, get together	0		4	18.2	3	14.3	3	18.8
Something else	0		1	4.5	1	4.8	0	
Negative memory								
Self, guild, shame	4	16.7	2	9.1	3	14.3	1	6.3
Partner, ending of relation, or relationship troubles	7	29.2	6	27.3	8	38.1	4	25
Friends that are not being supportive, or do not show respe	4	16.7	6	27.3	3	14.3	4	25
Friends, having words with, or being critisized by	1	4.2	0		2	9.5	1	6.3
Parents do not show support/ apsreciation	3	12.5	1	4.5	1	4.8	5	31.3
Having words/being critisized with /by strangers	0		1	4.5	0		0	
Loss, or illness	3	12.5	6	27.3	3	14.3	1	6.3
Something else	2	8.3	0		1	4.8	0	

less than 5% of cases. However, the number of cases in each group is too small to perform non-parametric tests for these differences.

RATINGS OF AUTOBIOGRAPHICAL EVENTS

Overall, all subjects rated their negative autobiographical memories as being more stressful, more frightful, and less positive, compared to their positive autobiographical memories (all t's>2.19, P's< .001). In addition, all participants indicated that they thought less frequently about the negative memory (t(81)=-2.19, P<.05), compared to the positive autobiographical memory. Finally, there was no difference in reported vividness of the negative vs. positive memories (t(81)=.86, P=.39).

On a group level, it appeared that the four groups differed marginally on vividness of the negative autobiographical memory (F(3,78)=2.53, P=.08) with the Low CEM, Moderate CEM, and Severe CEM groups reporting to remember the negative autobiographical memory less vividly than the No Abuse group (Table 1).

The groups did not differ on all other ratings of the positive and negative autobiographical memory (all F's <2.17, P's> .10), Table 1.

INTRUSIONS OF NEGATIVE AND POSITIVE AUTOBIOGRAPHICAL MEMORIES DURING SUPPRESSION AND EXPRESSION PERIOD

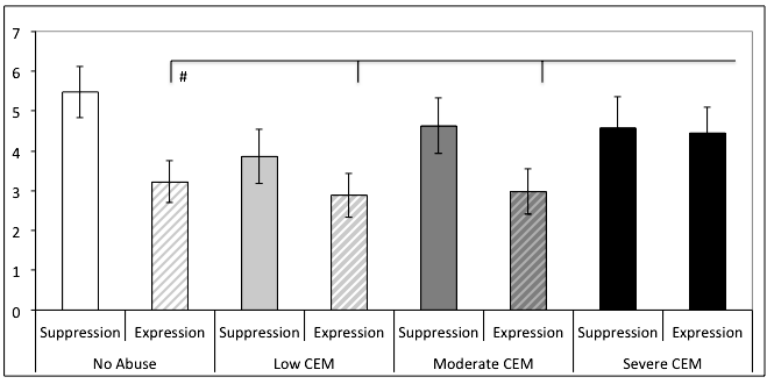
To investigate the impact of CEM on the number of intrusions of autobiographical memories, we conducted a Valence (positive-negative)×Phase (suppression-expression) RM ANCOVA with Group (No Abuse, Low-, Moderate-, Severe CEM) as fixed factor. To control for the group differences in total IES score, we added total IES score as covariate to the analysis.

The analysis showed that there was a significant Group×Phase interaction ($F(3,76)=3.23$, $P<.05$, $\eta p^2 = .11$)[II] indicating that the amount of intrusions in the groups differed for the suppression vs. expression phase (depicted in Figure 1). To further investigate this interaction, we performed exploratory contrast analyses. The CEM groups did not differ in the amount of self-reported intrusions during the suppression phase (all Contrast Estimates (CE)'s< 1.06, all P's> .39) However, during the expression phase, when participants were no longer instructed to suppress thinking about the memory, it appeared that individuals reporting Severe CEM reported (marginally) more intrusions compared to the No Abuse group (CE= -1.43, P=.08) to the Low CEM group (CE=-1.62, P=.06) and to the Moderate CEM group (CE=-1.60, P=.06) Finally, the amount of intrusions significantly decreased over time (from suppression to expression) for the No Abuse, Low CEM, or Moderate CEM groups (all t's>-2.64, P's<.05) However, the Severe CEM group did not show this decline of intrusions over time (t=-.50, P=.62) indicating that they reported a similar amount of intrusions during the suppression and expression phase.

In addition, Group did not have a main effect on self-reported intrusions ($F(3,76)=.78$, $P=.50$) and IES score was not a significant covariate in the analysis ($F(1,76)=2.64$, $P=.11$). Group did not interact with Valence ($F(3,76)=.77$, $P=.51$) indicating that the groups did not differ in the amount of intrusions for positive vs. negative autobiographical memories. There was no Group×Valence×Suppression interaction ($F(3,76)=1.07$, $P=.36$). All participants reported more intrusions in the suppression compared to the expression phase (i.e. a main effect of Phase ($F(1,76)=4.09$, $P<.05$, $\eta p^2 = .05$, see Figure 2).

[II] *Adding IES avoidance as covariate to the model (instead of IES total), or adding frequency of thinking about the negative event, or adding vividness of the negative events as covariate to the model did not affect the results, including the significant Group×Phase interaction.*

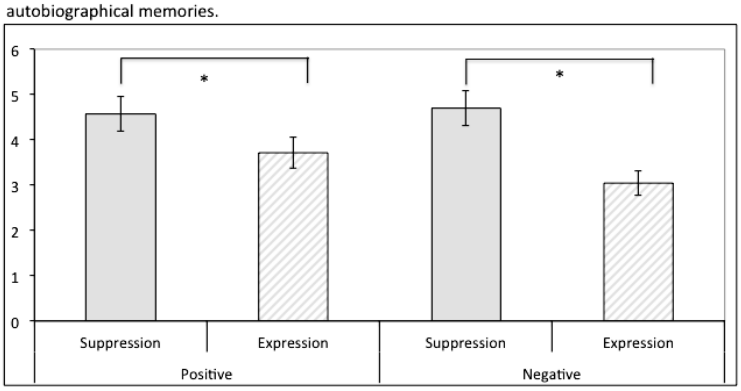
Figure 2. Mean and standard errors of self-reported intrusions of the autobiographical memories in the Suppression and Expression phase within the CEM groups.



Note, # = P<.10.

Hence, we found no post-suppressive rebound effect (Geraerts & McNally, 2008; Wenzlaff & Wegner, 2000). In addition, there was no main effect of Valence ($F(1,76)=.72$, $P=.40$), but there was a significant Valence×Phase interaction ($F(1,76)=6.86$, $P<.05$, $\eta p^2 = .08$). Taken together, all participants reported fewer intrusions in the expression phase, and that effect was stronger for the negative autobiographical memories (Figure 3).

Figure 3. Mean and standard error of self reported intrusions for the positive and negative autobiographical memories.



Note. * = P < .05.

For all participants, correlation analyses showed that self-reported tendency to have intrusions about a negative life event (i.e. IES Intrusions), correlated marginally with the actual amount of self-reported negative autobiographical event intrusions during the thought suppression task (i.e. during suppression (r= .19, P=.10), and expression (r=.19, P=.09)). Moreover, tendencies to not think about that negative life event on the IES Avoidance did not correlate with the amount of self-reported intrusions of a

negative autobiographical event during the thought suppression task (i.e. suppression and expression, *r*'s<.12, P's>.44).

In contrast, the amount of intrusions of the negative autobiographical memory was strongly correlated with general distress (as measured with the SCL-90), both during the suppression (*r*=.41, P<.001) and expression phase (*r*=.40, P<.001). In addition, self-reported intrusions of the positive autobiographical memory also correlated somewhat to general distress, significantly during the suppression phase (*r*=.32, P<.01) and marginally significantly during the expression phase (*r*=.21, P=.06).

Discussion

This study aimed to investigate the impact of varying degrees of CEM on intrusions during suppression of and when no longer instructed to actively suppress, positive and negative autobiographical memories. We found no group differences when participants were instructed to suppress thinking about their memory. Thus, individuals with Severe CEM were not more adept in actually suppressing their negative autobiographical memory. However, during the expression phase, when participants were no longer instructed to actively suppress thinking about their autobiographical memory, individuals reporting No Abuse, Low, and Moderate CEM reported fewer intrusions of both positive and negative memories than participants reporting Severe CEM. These findings indicate that there is no dose-response relationship between CEM severity and number of intrusions, rather, only the most affected individuals, those reporting severe CEM, reported a differential amount of intrusions during the expression phase. Furthermore, and in line with Krause et al. (2003), we found that individuals reporting Severe CEM are characterized by higher scores on the avoidance scale (as measured with the IES) in response to negative experiences. Finally, we found that the number of actual intrusions during the thought suppression task had a strong relationship with general distress, which was especially prominent for the negative autobiographical memory (this is in line with; Dalgleish & Yiend, 2006; Kashdan, Barrios, Forsyth, & Steger, 2006; Krause et al., 2003).

Our findings show that individuals reporting No Abuse, Low CEM, or Moderate CEM report fewer post-suppressive intrusions than individuals reporting Severe CEM. The amount of intrusions significantly decreased over time (from suppression to expression) for the No Abuse, Low CEM, or Moderate CEM groups. However, the Severe CEM group did not show this decline of intrusions over time, they reported a similar amount of intrusions during the suppression and expression phase. One of the explanations for this finding may be that the severe CEM group shows sustained intrusions in response to emotional memories. Perhaps these emotional autobiographical memories require more processing time in individuals reporting CEM, and therefore continue to intrude. Another explanation may be that the severe CEM group was unsuccessful at diverting their thoughts, while the other groups were successful at not thinking about the memory. A third

explanation may be that individuals reporting Severe CEM involuntary persist in active suppression of these memories, even when they are not instructed not to do so. An important reason for the perpetuation of suppression may be that individuals reporting CEM have negative self-associations (van Harmelen et al., 2010). Individuals who are extremely self-critical may perceive the rebound effects of thought suppression as personal failures, which may lead them to perpetuate active suppression (Kelly & Kahn, 1994; Wenzlaff & Wegner, 2000).

These findings may have implications for clinical interventions. Increased occurrences of a distressing memory or thought have been found to augment psychological distress (Dalgleish & Yiend, 2006; Kashdan, et al., 2006; Krause, 2003). Therefore, therapists working with individuals who report emotional maltreatment in their youth could teach their patients more effective types of mental control in order to suppress thinking about, or reduce negative arousal related to, negative autobiographical events, using for instance memory diversion techniques, acceptance-based interventions or interventions aimed at expressing the negative thoughts (Wenzlaff & Wegner, 2000). An example of a memory diversion technique is the think/no-think task, which has been proven a successful memory diversion tool to suppress thinking about unwanted memories (Anderson & Green, 2001). Alternatively, therapists could aim at reducing the negative emotionality of the memory, for instance by acceptance and expressing the thoughts through cognitive therapy.

For all participants, the number of intrusions during the thought suppression task was marginally related to the self-reported tendency to experience intrusions of a negative life event (IES Suppression), but not related to self-reported tendency to avoid thinking about a negative life event (IES Avoidance). In line, despite reporting more avoidant tendencies on the IES, individuals with Severe CEM were not more adept in actually suppressing their negative autobiographical memory. Moreover, while rating their autobiographical memories in the thought suppression task, individual reporting Severe CEM indicated to think as often about their negative autobiographical memory as individuals in the other groups. However, this was only the case during the suppression phase. When they were no longer instructed to avoid thinking about their memory, the other groups reported fewer intrusions than individuals with Severe CEM. Taken together, the thought suppression task may be a more sensitive instrument to measure tendencies to not think about distressing memories, and how successful these tendencies are, when compared to explicit (self-report) measures. This may be explained by the fact that explicit measurements are sensitive to inflation, or distortion, for instance because of acquiescence bias, or general distress (e.g. McNally, 2003). However, these findings may also be related to the fact that 69 individuals reported another negative experience for the IES as the thought suppression task, and only 13 individuals reported the same experience on both tasks (i.e. n=5 in the No

Abuse group, n=4 in the Low CEM, n=4 in the Moderate CEM, and n=1 in the Severe CEM group).

It is important to acknowledge that, contrary to an accumulating number of studies, we did not find evidence for an overall post-suppression rebound effect (Wenzlaff & Wegner, 2000). Our findings of higher frequency of intrusions during the suppression compared to the expression phase are more indicative of an immediate enhancement of the intrusions, especially for the negative autobiographical memory (Geraerts, Hauer, & Wessel, 2010; Salkovskis & Campbell, 1994). Studies investigating thought suppression under cognitive load also indicate immediate enhancement of intrusions during the suppression period (Dalgleish & Yiend, 2006), and no post-suppressive rebound of these memories (Wenzlaff & Wegner, 2000). In addition, emotional material is harder to suppress than neutral information (McNally & Ricciardi, 1996; Wenzlaff & Wegner, 2000). This is in line with findings that initial suppression of personally intrusive thoughts is followed by diminished expression of these thoughts (i.e. no rebound effect) (Kelly & Kahn, 1994; although this is not often been replicated; see Abramowitz, Tolin & Street, 2001 for a meta-analysis). A possible explanation for this finding is that individuals have more experience in distracting themselves from a personal thought. They may even have developed a network of distracter thoughts, and may have used this network in order to distract themselves during the suppression of a personal thought, and subsequently have diminished intrusions of that thought during the expression phase (Kelly & Kahn, 1994). In line, Salkovskis and Campbell (1994) found higher rates of intrusions of personal thoughts for participants who tried to suppress the thoughts compared to those who only monitored (expressed) them. Therefore, more intrusions during the suppression vs. expression phase may be indicative that individuals found it hard to actively suppress these positive and negative emotional autobiographical events, or that they had more experience with distracting themselves.

This study is not without its limitations. Although the overall sample is large, our sub samples were relatively small, limiting the types, and power of, statistical analyses that can be run. Furthermore, we did not include a baseline period prior to the suppression phase, which limits our interpretations regarding the effects of our instructions to suppress on the amount of reported intrusions. In addition, in the expression phase, the individuals were instructed to think about anything they wanted, including the autobiographical memory. Therefore, the expression phase more closely resembles day-to-day life when compared to the suppression phase. On the other hand, in our study, the expression phase always followed the suppression phase. In this way, we aimed to maximize our chances of measuring the post-suppression rebound effect. Although spontaneous suppression leads to the same paradoxical effects as instructed suppression (Wenzlaff & Wegner, 2000), in day to day life, individuals are not first explicitly instructed to suppress thinking about their memories. Therefore, our findings may only translate to explicit attempts to suppress thinking

about distressing memories (e.g. 'I must not think about this experience anymore').

It is important to acknowledge that the assessment of childhood trauma was based on retrospective self-report, and may therefore be susceptible to distortion and/or inflation (McNally, 2003). In addition, especially the inherent subjectivity of retrospective self-reported CEM is important to acknowledge. However, research has indicated that individuals are more likely to underreport than overreport their history of childhood abuse (Brewin, 2007). Furthermore, in a large sample of outpatients with depressive and anxiety disorders and healthy controls, current affective state did not moderate the association between retrospective self-reported CEM and lifetime affective disorders, indicating that recall of CEM is not critically affected by current mood state (Spinhoven et al., 2010).

CONCLUSION

We found that individuals reporting Severe CEM (vs. No Abuse, Low CEM, or Moderate CEM) report more avoidant tendencies for negative emotional experiences. Despite these tendencies, individuals reporting Severe CEM are not more adept in actually suppressing thinking of negative (and positive) autobiographical memories. Furthermore, we found that when individuals were no longer instructed to suppress thinking about the memory, individuals reporting No Abuse, Low CEM, or Moderate CEM reported fewer intrusions of both positive and negative autobiographical memories when compared to reporting Severe CEM. Finally, intrusions of negative memories are strongly related to psychiatric distress. Therefore, the present study results may provide an important avenue to better understand the consequences that emotional child maltreatment might have, as well as suggesting avenues for successful intervention.

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SECTION 2: THE IMPACT OF CHILDHOOD EMOTIONAL MALTREATMENT ON BRAIN STRUCTURE

Chapter 4: Reduced medial PreFrontal Cortex volume in adults reporting Childhood Emotional Maltreatment

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ABSTRACT

Childhood emotional maltreatment (CEM) has been associated with a profound and enduring negative impact on behavioral and emotional functioning. Animal models have shown that adverse rearing conditions, such as maternal separation, can induce a cascade of long-term structural alterations in the brain, particularly in the hippocampus, amygdala, and prefrontal cortex (PFC). However, in humans, the neurobiological correlates of CEM are unknown. 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 depression and/or anxiety disorders reporting CEM before the age of 16 (n=84, age: M=38.7) displayed structural brain changes compared to controls and patients who report no childhood abuse (n=97, age: M=36.6). We found that self-reported CEM is associated with a significant reduction in predominantly left dorsal medial prefrontal cortex (dmPFC) volume, even in the absence of physical and/or sexual abuse during childhood. In addition, reduced dmPFC in individuals reporting CEM is present in males and females, and independent of concomitant psychopathology. In this study, we show that CEM is associated with profound reductions of mPFC volume, suggesting that sustained inhibition of growth or structural damage can occur after exposure to CEM. Given the important role of the mPFC in the regulation of emotional behavior, our finding might provide an important link in understanding the increased emotional sensitivity in individuals reporting CEM.

INTRODUCTION

Every year, about one in ten children growing up in Western societies experiences Childhood Emotional Maltreatment (CEM; Egeland, 2009; Gilbert et al., 2009). Emotional maltreatment encompasses any act of commission (i.e. verbal abuse) or omission (i.e. emotional neglect) that is (potentially) harmful, or insensitive to the child's emotional development (Egeland, 2009; Gilbert et al., 2009), and has been associated with a profound and enduring negative impact on behavioral, emotional, and social functioning (Egeland, 2009; Gilbert et al., 2009). For instance, CEM is associated with maladaptive emotional functioning in adulthood (Teicher, Samson, Polcari, & McGreenery, 2006), which in turn is a key vulnerability factor for the development of psychiatric disorders when faced with stressors in later life (Beck, 2008). In line with this, CEM is an important predictor for the development of depressive and anxiety disorders in adulthood (Gibb, Benas, Crossett, & Uhrlass, 2007; Spinhoven et al., 2010). However, the neurobiological correlates underlying the emotional sensitivity in individuals reporting CEM are yet unknown.

In animals, adverse rearing environments such as maternal separation, loss, or isolation rearing induce a cascade of long-term alterations on the level of cognitive functioning, hypothalamic-pituitary (HPA) axis functioning, (immediate) gene expression and brain morphology (Sánchez, Ladd, & Plotsky, 2001). Structural alterations in the brain include reduced dendrite length, dendritic branching, spine density, and suppression of neurogenesis, and have predominantly been observed in limbic structures (amygdala, hippocampus) and prefrontal cortex (PFC)(Arnsten, 2009; Lupien, McEwen, Gunnar, & Heim, 2009; McEwen, 2008; Sánchez et al., 2001). In line, human studies examining the neuroanatomical correlates of childhood maltreatment in adults found decreased gray matter (GM) volume in the hippocampus (Kitayama, Vaccarino, Kutner, Weiss, & Bremner, 2005; Vythilingam et al., 2002), and medial (m)PFC (Andersen et al., 2008; Cohen et al., 2006; Frodl et al., 2010; Tomoda et al., 2009; Treadway et al., 2009). However, these studies focused mainly on the impact of sexual (Andersen et al., 2008; Kitayama et al., 2005; Vythilingam et al., 2002) and/or physical abuse (Tomoda et al., 2009), or did not exclude co-occurrence of different types of abuse (Cohen et al., 2006; Frodl et al., 2010; Treadway et al., 2009).

One way through which chronic stress may lead to structural changes is by means of enhanced activation of neuroendocrine systems (McEwen, 2008). During chronic stress, increased secretion of glucocorticoids (i.e. the stress hormone cortisol in humans) interferes with the transcriptional mechanisms that control the expression of brain-derived neurotrophic factor (BDNF), a growth factor that has been linked to neuronal proliferation and plasticity (McEwen, 2008; Nestler et al., 2002). In this way, chronic stress may inhibit cytogenesis and increase vulnerability to attrition within the hippocampus, amygdala and/or PFC (e.g. Lupien et al., 2009; McEwen, 2008). In line with these findings, childhood maltreatment has been linked to enhanced cortisol reactivity to psychosocial stress in patients with

depression and anxiety disorders (Elzinga, Spinhoven, Berretty, De Jong, & Roelofs, 2010; Heim, 2000; Heim et al., 2002) and to blunted cortisol reactivity in healthy subjects (Carpenter et al., 2007). Additionally, altered patterns of cortisol reactivity during stress have been found in individuals reporting CEM (Carpenter et al., 2009; Elzinga et al., 2010). Furthermore, white matter (WM) tract abnormalities were found in a small sample of young adults reporting CEM (n =16; Choi, Jeong, Rohan, Polcari, & Teicher, 2009). However, it is yet unknown whether CEM is similarly associated with structural GM abnormalities in adulthood. Given the important role of the limbic brain regions (hippocampus and amygdala) and the mPFC in the perception and regulation of emotional behavior and stress response (Arnsten, 2009; Cardinal, Parkinson, Hall, & Everitt, 2002; Lupien et al., 2009; McEwen, 2008), GM abnormalities in (one of) these regions might underlie the maladaptive emotional functioning associated with CEM.

Therefore, we sought to investigate the effect of CEM on adult brain morphology in unmedicated patients currently diagnosed with depression and/or anxiety disorder and healthy controls (HCs). We used high resolution Magnetic Resonance Imaging (MRI) and a whole-brain optimized Voxel Based Morphometry analysis approach, and specified the amygdala, hippocampus, and mPFC (medial prefrontal gyrus and anterior cingulate gyrus) as Regions of interest (ROI). We examined whether adult patients and HCs reporting multiple incidents of CEM before the age of 16 (n=84) displayed structural brain changes in comparison to patients and HCs who did not report a history of childhood abuse (n=97). In addition, to examine whether these structural brain changes are related to the development of psychopathology, we investigated whether these brain alterations were more apparent in individuals with a depression and/or anxiety disorder compared to individuals who never developed a depression and/or anxiety disorder.

METHODS

THE NESDA –MRI STUDY

Participants were drawn from the Netherlands Study of Depression and Anxiety (NESDA), (N=2981), a large cohort study (Penninx et al., 2008). A subset of the NESDA participants (both patients and HCs) was selected to undergo MRI scanning for the NESDA MRI study. Inclusion criteria for patients in the NESDA-MRI study were: current major depressive disorder (MDD) and/or anxiety disorder (ANX; panic disorder (PD) and/or social anxiety disorder (SAD) and/or Generalized Anxiety Disorder (GAD) in the last 6 months according to DSM-IV criteria). Diagnoses were established using the structured Composite International Diagnostic Interview (CIDI: Wittchen et al., 1991), administered by a trained interviewer. Exclusion criteria were: the presence of axis-I disorders other than MDD, PD, SAD or GAD; any use of psychotropic medication other than a stable use of selective serotonin reuptake inhibitors (SSRI) or infrequent benzodiazepine use [3

times 2 tablets weekly, or within 48 hrs prior to scanning]. Additional exclusion criteria for both patients and HCs were: the presence or history of major internal or neurological disorder; dependency or recent abuse [past year] of alcohol and/or drugs; hypertension (>180/130mm Hg); heavy smoker (>5 cigarettes/day); and general MR-contra indications. HCs had no lifetime depressive or anxiety disorders and were not taking any psychotropic drugs. Eventually, 301 native Dutch speaking participants (235 patients and 66 HCs) were included and underwent MR imaging in one of the three participating centers (i.e. Leiden University Medical Center [LUMC], Amsterdam Medical Center [AMC], and University Medical Center Groningen [UMCG]). The Ethical Review Boards of each participating center approved this study. All participants provided written informed consent.

Clinical assessments

In the NESDA study, childhood maltreatment was assessed with the Nemesis trauma interview (De Graaf, Bijl, Smit, Vollebergh, & Spijker, 2002). In this interview, respondents were asked whether they had experienced emotional neglect, psychological abuse, physical abuse and/or sexual abuse before the age of 16, how often this had occurred (i.e. never, once, sometimes, regularly, often, or very often), and what their relationship with the perpetrator was. Emotional neglect was described as: 'people at home didn't listen to you, your problems were ignored, and you felt unable to find any attention or support from the people in your house'. Psychological abuse was described as: 'you were cursed at, unjustly punished, your brothers and sisters were favoured – but no bodily harm was done'. CEM was defined as multiple incidents (>once) of emotional neglect and/or emotional abuse before the age of 16 years, because we assumed that only multiple incidents of emotional abuse and/or emotional neglect might be associated with neuroanatomical changes. Overall CEM frequency was defined as the most frequent occurrence as reported (e.g. if psychological abuse occurred often, and emotional neglect sometimes, overall CEM score is often).

Negative life events were assessed using the List of Threatening Events Questionnaire (LTE-Q; Brugha, Bebbington, Tennant, & Hurry, 1985). In addition, at the day of scanning, depression and anxiety severity was measured using the Montgomery Åsberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) and the Becks Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988).

Additional exclusion criteria

High resolution anatomical images were obtained from 291 participants (imaging data from 10 participants were excluded because of poor image quality). Additionally, two healthy controls were excluded from the NESDA-MRI study because of MADRS scores that were indicative of possible depressive symptomatology at the day of scanning (MADRS>8; Müller, Szegedi, Wetzel, & Benkert, 2000). For the present study, individuals using SSRIs were excluded (n=79) given their potential effect on neuronal

plasticity (e.g. Dranovsky & Hen, 2006). Additionally, individuals reporting physical or sexual abuse but no CEM were also excluded (n=5). Finally, individuals reporting only a single incident of CEM (n=24) were excluded. Our final sample (n=181) consisted of 84 participants reporting CEM, and 97 participants that reported No Abuse.

THE CEM AND NO ABUSE GROUPS

The CEM group consisted of participants who reported emotional neglect or psychological abuse during childhood hat had occurred sometimes, regularly, often or very often (n=84, i.e. MDD (n=20), ANX (n=21), Comorbid Depression and Anxiety disorder ([CDA] n=30), and HC (n=13), of whom 36 participants also reported childhood physical and/ or sexual abuse, see Table 1). The No Abuse group consisted of individuals who did not report CEM, physical or sexual abuse (n=97; i.e. MDD (n=22), ANX (n=22), CDA (n=13), and HC (n=40)). In the CEM group, 96.4 % (n=81) of the participants reported emotionally neglect, whereas 57.1 % (n=48) reported to have been psychologically abused, and 54% (n=45) reported both emotional neglect and psychological abuse. In addition, 97.6 % reported that the individual's biological parents were the perpetrators of CEM (n=82).

Table 1. Clinical and demographic characteristics of participants reporting Childhood Emotional Maltreatment vs. No Abuse

		No Abuse (*n*= 97)	CEM (*n*= 84)	F	U	X^2	P
Gender	% M/ F	33/ 67	34.5/ 65.5			.05	.83
Age	Mean (SEM)	36.57 (1.09)	38.68 (1.09)	1.86			.17
Education	Mean (SEM)	13.27 (0.29)	12.81 (0.35)		3706.5		.29
Handedness	% L/ R	11/ 89	5/95			2.56	.11
Current diagnosis	*n* MDD	22	20			.09	.76
	n ANX	22	21			.02	.88
	n CDA	13	30			6.72	.01
	n HC	40	13			13.75	.00
Lifetime diagnosis	% MDD	43.29	77.38			25.64	.00
	% ANX	41.24	67.86			12.83	.00
MADRS	Mean (SEM)	7.10 (.94)	14.45 (1.89)		2272.5		.00
BAI	Mean (SEM)	8.79 (1.04)	12.85 (1.08)		2651.5		.00
Scan location	% A/ L/ G	28.9/ 41.2/ 29.9	38.1/ 38.1/ 23.8			1.89	.39
Frequency of CEM	%S/R/O/V	0	10.8/ 37.4/ 21.7/ 30.1				
Concurrent abuse	*n* Physical	0	15				
	n Sexual abuse	0	8				
	n Physical and Sexual abus	0	13				
Gray Matter	Mean (SEM)	740.40 (7.98)	721.78 (7.33)	2.89			.09
White matter	Mean (SEM)	491.33 (6.94)	494.69 (6.53)	.12			.73

Note. CEM= Childhood Emotional Maltreatment, ANX= Anxiety Disorder, MDD= Major Depressive Disorder, CDA = Comorbid Depression and Anxiety Disorder, S=sometimes, R=regularly, O=often, V= very Often, A= Amsterdam Medical Center, L= Leiden University Medical Center, G= University Medical Center Groningen, MADRS= Montgomery Åsberg Depression Rating Scale, BAI= Beck Anxiety Inventory, F,U, X^2 = F ratio, Mann Whitney U statistic, and Chi-square test statistic, SEM= Standard Error of Mean.

MRI

Image Acquisition

Imaging data were acquired using Philips 3T MR-systems located at the participating centers, equipped with a SENSE-8 (LUMC and UMCG) and a SENSE-6 (AMC) channel head coil. For each subject an anatomical image was obtained using a sagittal 3D gradient-echo T1-weighted sequence (TR: 9 ms; TE: 3.5 msec; matrix 256×256; voxel size: 1×1×1 mm; 170 slices). Each scanning session also included several fMRI runs, both 'resting-state' and task-related. These results, as well as those of VBM comparisons between diagnostic groups (irrespective of childhood maltreatment), will be reported elsewhere.

Image preprocessing

An optimized Voxel Based Morphometry (VBM) approach following the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL; Ashburner, 2007) was performed using SPM5 (Statistical Parametric Mapping software; http:// www.fil.ion.ucl.ac.uk/spm/) implemented in Matlab 7.1.0 (The MathWorks Inc., MA, USA). VBM-DARTEL preprocessing included the following steps; 1) manually reorientation of the images to the anterior commissure, 2) segmentation of the anatomical images using the standard segmentation option implemented in SPM5, 3) applying the DARTEL approach for registration, normalization, and modulation, leaving the images in DARTEL space. In this approach, a DARTEL template is created based on the deformation fields that are produced by the segmentation procedure. Next, all individual deformation fields are warped (and modulated) to match this template. 4) Smoothing of the gray matter (GM) and white matter (WM) images using an 8mm, full width at half maximum, Gaussian kernel to increase signal to noise ratio. In the resulting GM images, each voxel represents an absolute amount of GM volume, equivalent to the GM volume per unit prior to normalization.

VBM analysis

GM (or WM) segments in native space were used to calculate absolute total GM (or WM) volumes. Next, smoothed GM (WM) density images were entered into a voxel by voxel analysis of variance for between-group comparisons, with age and total absolute GM (or WM) as covariate to correct for total brain volume. Effect of center was added by means of two dummy variables as extra regressors in all analyses. To get maximal sensitivity, and to optimize voxel residual smoothness estimation and to exclude false positives in non-GM (or WM) tissue, voxel-wise comparisons were masked using a comparison-specific explicit optimal threshold GM (or WM) mask created using the Masking toolbox (Ridgway et al., 2009).

For the a priori set ROIs (mPFC, amygdala and hippocampus), we set a threshold of $P<.001$, uncorrected, with a spatial extent threshold of 50 contiguous voxels for group interactions. To further protect against Type I error, Small Volume Correction (SVC) was applied, by centering a sphere of

16 mm around the peak voxel. The resulting Volumes of Interest had to meet P<.05, FWE voxel corrected, to be considered significant (i.e. Z>3.50). For regions not a priori specified, a voxel level threshold of P<.05 whole brain FWE corrected was set. If significant group differences were observed in the VBM analysis, we then exported the volume of the significant clusters (i.e. K centered around the peak voxel) per subject to SPSS. Clinical and demographic group differences were analyzed using SPSS-17 (www.spss.com), and in all analyses, age, total GM (WM) volume, and dummy regressors for the scan centers were included as covariates.

RESULTS

THE NEUROANATOMICAL CORRELATES OF CHILDHOOD EMOTIONAL MALTREATMENT

To investigate the neuroanatomical correlates of CEM, we first set up a VBM analysis to compare the GM density maps/images of individuals reporting CEM (n=84) with GM density maps of the No Abuse group (n=97). These analyses revealed that CEM was associated with a 5.14 % reduction in the left dorsal mPFC (x=-11 y=23 z=40, Brodmann Area (BA) 8, cluster size/ number of voxels (K) =263, Z=3.80, P<.05, Small Volume Corrected (SVC), Table 2). No significant differences were observed in hippocampus or amygdala, or in other brain regions. Only at a very low threshold was CEM was associated with reduced right posterior hippocampal volume (x=29 y=-35 z=-6, Z=2.06, n.s). Additionally, CEM was not associated with a significant increase in regional GM volumes. Finally, CEM was not associated with WM reductions in or surrounding our ROIs, or with increased regional GM volume.

To explore possible interactions between CEM, current diagnosis, and gender, a 2 (CEM)×4 (diagnosis: MDD, ANX, CDA, and HC)×2 (gender) univariate ANCOVA was performed, with local mPFC volume (ml.) as a dependent factor. Again, individuals from the CEM group had smaller mPFC volumes than the No Abuse group (CEM (M± SEM): 4.80 ± .06 ml. vs. No Abuse; 5.06 ± .06 ml. (F(1, 161)= 12.36, P<.01, Cohen's d (d) =.53). Interestingly, there was no interaction between CEM and diagnosis (F(3,161)=. 45, P=.72, d=.01), and post-hoc analyses indicated that the mPFC reductions are present in all groups, even though the numbers were relatively small for such comparisons [one sided: MDD (F(1,34)=8.65, P<.01, d=.93), ANX (F(1,35)=2.55, P=.06, d=.50), CDA (F(1,35)=2.63, P=.06, d=.55), and HC (F(1,45)=1.85, P=.09, d=.44)]. In addition, there was no interaction between CEM and gender (F(1,161)=2.01, P=.99, d=.21). Taken together, these results indicate that reduced mPFC volume was present in all CEM groups (i.e., male and female individuals with MDD, ANX, CDA, and in the HC group). Moreover, similar results were obtained when depression and

anxiety severity were added as covariates (F(1,155)=12.41, P<.01, d=.53)[III], indicating that our results cannot be explained by the presence of more severe depressive and/or anxious symptomatology amongst individuals reporting CEM.

NEUROANATOMICAL CORRELATES OF ISOLATED EMOTIONAL MALTREATMENT IN CHILDHOOD.

To exclude the possibility that our results are driven by concurrent history of physical and/or sexual abuse in some of the participants, we conducted a whole brain VBM analysis to compare the GM density maps of individuals reporting only CEM (n=48; MDD (n=13), ANX (n=12), CDA (n=13), and HC (n =10) see Table S1) with individuals reporting No Abuse (n=97). In this analysis the 36 individuals who also reported childhood physical and/or sexual abuse were excluded. This analysis showed that individuals reporting only CEM had a volume reduction of 7.2 % in left and right (although predominantly left) dorsal medial mPFC (x=-11 y=21 z=40, BA 8, K=767, Z=4.37, P<.05 (SVC), see Table 2), extending into the anterior mPFC and anterior cingulate gyrus (Figure 1, Table 2).

Table 2. The neuroanatomical correlates of the Childhood Emotional Maltreatment vs. No Abuse.

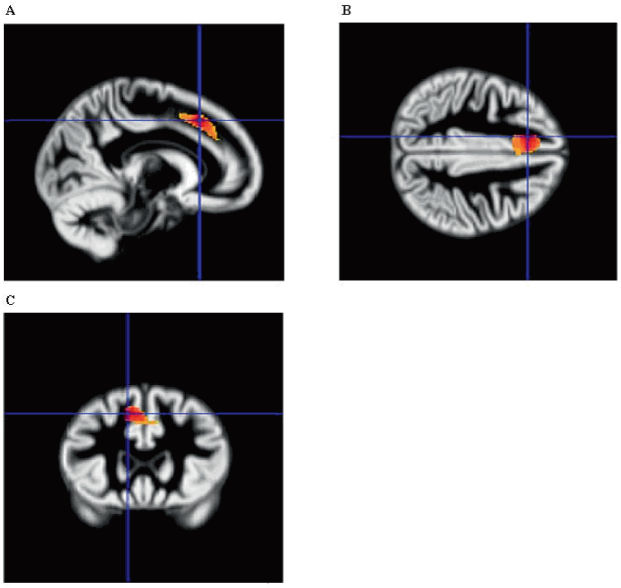
						DARTEL -coordinates			
		R/L	BA	region	K	x	y	z	Z
CEM (*n* =97) vs. No Abuse (*n* =84)	CEM< No Abuse	L	8	Medial prefrontal gyrus	263	-11	23	40	3.80 **
only CEM (n=48) vs. No Abuse (n=97)	CEM< No Abuse	L+R	8	Medial prefrontal gyrus	767	-11	21	40	4.37 **
						-5	9	42	
						6	18	36	
		R	9/32	Cingulate gyrus/medial prefrontal	87	9	44	16	3.53 **
		R	10/32	Cingulate gyrus/medial prefrontal		11	47	9	

Note. CEM= Childhood Emotional Maltreatment, R=right sided, L=Left sided, BA= Brodmann Area, K= cluster size (number of voxels), **=P<.05, SVC 16 mm FWE corrected.

Furthermore, no hippocampal, or amygdalar differences were observed, nor decreases in other brain regions. Again, only at a very low threshold was CEM associated with reduced right posterior hippocampal volume (x=29 y=-35 z=-6, Z=2.45, n.s). Finally, CEM was not associated with WM reductions in or surrounding our ROIs, or with increased regional GM volume.

[III] Four participants were missing because of incomplete depression or anxiety data (one reported CEM).

Figure 1. The medial PFC region showing 7.2 % volume reduction amongst individuals reporting only childhood emotional maltreatment displayed on a sagittal (A), transversal (B) and coronal (C) plane.



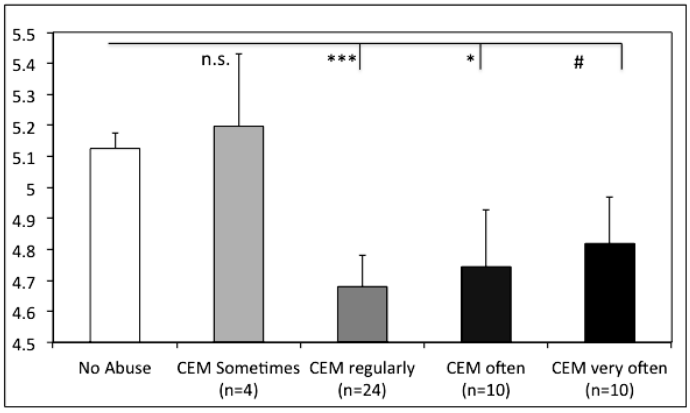
An ANCOVA confirmed the main effect of CEM (i.e. CEM: M ± SEM: 4.78 ± .07 ml., No Abuse: 5.15 ± .06 ml., (F(1,125=15.15, P<.001, d=.69). Moreover, the reduced mPFC volume was present in all CEM groups and in both male and female individuals (i.e. no interaction was found with diagnosis (F(3,125)=.27, P=.85, d=.09), and even within these small groups post-hoc analyses revealed a (marginally) significant (one–sided) impact of CEM only on mPFC volume ((i.e. MDD, (F(1,27)=7.72, P<.01, d=1), ANX (F(1,26)=2.93, P<.05. d=.63), CDA (F(1,18)=3.20, P<.05, d=.73), and HC (F(1,42)=1.96, P=.08, d=.51)). Moreover, CEM did not interact with gender (F(1,125)=.08, P=.78, d=.05). These results could not be explained by higher symptom severity amongst individuals reporting CEM, since similar results were obtained when depression and anxiety severity were added as covariates (F(1,116)=15.72, P<.001, d=.70[IV]).

[IV] *History of alcoholism (abuse or dependence as measured with the CIDI) did not affect the results (i.e. history of alcoholism (yes or no) was not a significant covariate in the analysis (F(1,124) =1.76, P=.19), nor did it impact the main effect of CEM on mPFC volume (F(1,124) =15.98, P<.000, d=.71)).*

ASSOCIATIONS BETWEEN FREQUENCY OF EMOTIONAL MALTREATMENT AND MPFC VOLUME

To investigate whether the mPFC volume reductions were dependent on CEM frequency, we performed a 5 (frequency of CEM: no abuse, sometimes, regularly, often, and very often) × 4 (diagnosis: MDD, ANX, CDA, and HC) ANCOVA, with local mPFC volume (ml.) as a dependent factor. The analysis revealed a main effect of frequency of CEM on mPFC volume ($F(4,120)=4.89$, $P<.001$, $d=.39$)-, which did not interact with psychopathology ($F(12,120)=.93$, $P=.52$, $d=.17$). As is illustrated in Figure 2, mPFC volumes were reduced in individuals reported that CEM happened regularly or more often. Individuals reporting CEM sometimes did not have a significantly lower mPFC volume when compared to the No Abuse group, however, this group was extremely small (n=4)[V] therefore caution is warranted when interpreting the findings of these individuals.

Figure 2. Estimated Marginal Means and Standard Error of Mean (SEM) of medial PreFrontal Cortex (mPFC) volume amongst the different frequencies of Childhood Emotional Maltreatment (CEM), and contrast results of CEM frequencies vs. the No Abuse group.



Note. ***= P<.000, * = P<.05, # = P=.056, n.s. = not significant (two-sided).

[V] *Exclusion of the 'sometimes' group (n=4), due to its small size, did not affect the results, including the main effect of CEM on mPFC volume ($F(1,120)=15.8$, $P<.000$, $d=.73$).*

DISCUSSION

In this study, self-reported CEM was found to be associated with a significant reduction in predominantly left dorsal mPFC GM volume, independent of gender, and psychiatric status, at least in individuals who reported CEM regularly, or more frequent. Furthermore, the mPFC GM volume reduction was not due to concomitant childhood physical and/or sexual abuse, as the reductions were also found when CEM was experienced in absence of concurrent childhood physical and/or sexual abuse.

These findings provide an important clinical extension of pre-clinical observations that the mPFC is highly sensitive to the effects of chronic stress in childhood (Arnsten, 2009; Lupien et al., 2009; McEwen, 2008). The mPFC is one of the brain regions that undergo major developmental changes during childhood and adolescence (Arnsten, 2009; Lupien et al., 2009). Exposure to emotionally abusive episodes during this developmental time period may increase secretion of glucocorticoids, which may interfere with the transcriptional mechanisms that control the expression of BDNF, and may thereby inhibit cytogenesis and increase vulnerability to attrition within the mPFC (Arnsten, 2009; Lupien et al., 2009; McEwen, 2008; Nestler et al., 2002). Moreover, the fact that reductions in hippocampal volume were only observed at a very low threshold, and no significant changes were observed in the amygdala, concurs with findings of animal models on isolation rearing or maternal separation that indicate a specific and profound impact on the mPFC (Levine et al., 2008; Sanchez et al., 2007), in comparison to the hippocampus and amygdala (Schubert, Porkess, Dashdorj, Fone, & Auer, 2009). For example, in animals, it has been shown that architectural changes in prefrontal dendrites can already be observed after only one week of stress, or even after a single stressful incident (Arnsten, 2009). In contrast, structural changes in the hippocampus only appear after several weeks of stress, which might be an indication that the mPFC is more sensitive to the detrimental effects of stress (Arnsten, 2009).

The finding that CEM is associated with (predominantly left) dorsal mPFC reduction is of particular interest when considering the fact that the mPFC plays an important role in emotion regulation (Cardinal et al., 2002; Phillips, Drevets, Rauch, & Lane, 2003). Moreover, reduced activity in the left PFC has been particularly associated with negative emotional states (Demaree, Everhart, Youngstrom, & Harrison, 2005). Furthermore, the dorsal mPFC is essential for the regulation of autonomic and neuroendocrine stress response and arousal associated with emotional states and behavior, while the ventral mPFC has been implicated in generating these emotional states and behaviour (Phillips et al., 2003; Radley, Williams, & Sawchenko, 2008). The dorsal and ventral mPFC are reciprocally functionally related, and abnormalities in the function of either, or both, may be associated with abnormalities in emotional behavior and regulation (Phillips et al., 2003). In line with these findings, decreased blood flow in the dorsal mPFC has been associated with increased autonomic responsiveness, anxiety, and sad mood

(Phillips et al., 2003). In addition, mPFC dysfunctions have been implicated in many psychiatric disorders, including depressive disorders (Drevets, Price, & Furey, 2008) and anxiety disorders (Zhao et al., 2007). Taken together, these results suggest that the reduced dorsal mPFC volume may (partly) underlie the enhanced emotional sensitivity associated with CEM. It should be noted that, contrary to our predictions, the reduced mPFC volume associated with CEM was independent of psychopathological status, indicating that the reduced mPFC volume was not only present in individuals with psychopathology, but also in HCs who never developed a depression or anxiety disorder (even though the number of HCs with reported CEM is relatively small, and effect sizes of mPFC reductions were also smaller in the HCs than in individuals with depression and/or anxiety). Therefore, reduced mPFC volume does not seem to be directly linked to the development of depressive and/or anxiety disorders in individuals reporting CEM. This finding is more consistent with the idea that additional risk factors, such as genetic make-up (Frodl et al., 2010; Gatt et al., 2009; Joffe et al., 2009) alone, or in interaction with exposure to stressful life events during adulthood may additionally determine who will subsequently develop a depressive and/or anxiety disorder (Beck, 2008; Caspi & Moffitt, 2006). In line with this suggestion, individuals with current depressive and/or anxiety disorder reporting CEM (n=65) indeed reported more negative life events (Mean ± SEM: 5.96 ±.55) than HCs reporting CEM (n=13; 4.62 ±.24), ($t(76)=-2.26$, $P<.05$).

Although the present results are compelling, several potential limitations must be taken into account. The use of (DARTEL-) VBM approaches is not without its limitations (Ridgway et al., 2008), although recent studies (McLaren, Kosmatka, Kastman, Bendlin, & Johnson, 2010; Yassa & Stark, 2009) demonstrated that the DARTEL approach is an improvement to standard voxel-based approaches. In addition, the sensitivity of the DARTEL approach for detecting hippocampal atrophy has been demonstrated in MDD patients (Bergouignan et al., 2009). Nevertheless, manual tracing or shape based analyses techniques, as have been used in most previous studies on hippocampal structural abnormalities, might be more sensitive in detecting deformations compared to an automated segmentation approach. Furthermore, although a clinically diagnosed PTSD diagnosis was an exclusion criterion for NESDA, unidentified current or lifetime PTSD symptoms may still have been present, which may have influenced our findings. However, CEM related mPFC GM reductions were also present amongst HCs who had never developed a depressive or anxiety disorder; therefore, it is unlikely that current or lifetime PTSD may have confounded our results. In addition, history of childhood maltreatment was retrospectively assessed by means of an interview, and it is important to acknowledge the inherent subjectivity of self-reported CEM. For instance, the retrospective assessment of CEM may be subject to recollection bias, so that individuals with current psychopathology may over-report, whereas HCs may under-report a history of childhood maltreatment. However, we

would like to note that in the NESDA sample, current affective state did not moderate the association between CEM and lifetime affective disorder, indicating that recall of CEM in the current sample was not critically affected by current mood state (Spinhoven et al., 2010). Finally, our findings are based on a cross-sectional study. Whereas the idea that CEM is associated with mPFC GM volume reductions fits very well with numerous preclinical studies, the possibility of reversed causality cannot be excluded. For instance, individuals with reduced mPFC volume might report more CEM as a result of impaired emotion regulation. Another explanation may be that the reduced mPFC volume was pre-existent, and that inadequate emotion regulation associated with reduced mPFC volume might even increase children's risk for exposure to CEM. Following this line of thought, one would expect that reports of presence or absence of life stressors later in life would also be related to mPFC volume. Nevertheless, presence of life stressors (yes/no) was not associated with mPFC volume ($F(1,109)=.09$, $P=.76$, $d=.05$), and the impact of CEM on mPFC volume remained unchanged when adding presence of life events into the analysis ($F(1,109)=9.08$, $P<.01$, $d=.54$). Theoretically, longitudinal studies examining neuroanatomical developmental changes over time amongst individuals reporting CEM are needed to shed more light on the etiology of our findings. To the best of our knowledge, such studies have not yet been conducted, and from an ethical point of view it would be highly problematic to prospectively follow children that are known to be exposed to CEM without interfering in their situation.

CONCLUSION

We found in a large sample of un-medicated adults that self-reported CEM is associated with a substantial reduction in mPFC GM volume. In line with an accumulating number of animal studies (Levine et al., 2008; Lupien et al., 2009; Sánchez et al., 2001; Sanchez et al., 2007), our finding suggests that sustained inhibition of growth, or even structural damage, can occur after exposure to emotional maltreatment in childhood. In addition, previous studies have shown that CEM is associated with altered HPA axis reactivity to stress (Carpenter et al., 2009; Elzinga et al., 2008), and that CEM is an important predictor for the development of depressive and anxiety disorders in adulthood (Gibb et al., 2007; Spinhoven et al., 2010). Given the important role of the mPFC in the perception and regulation of emotional behavior and stress responses (Arnsten, 2009; Cardinal et al., 2002; Lupien et al., 2009; McEwen, 2008; Phillips et al., 2003; Radley et al., 2008; Sánchez et al., 2001), our finding might provide an important link in understanding the increased emotional sensitivity in individuals reporting CEM.

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Table S1. Clinical and demographic characteristics of participants reporting only Childhood Emotional Maltreatment vs. No Abuse.

		No Abuse (n=97)	only CEM (n=48)	F	U	X^2	P
Gender	% M/ F	33/ 67	42/ 58			1.05	.30
Age	Mean (SEM)	36.57 (1.09)	37.6 (1.60)	.29			.59
Education	Mean (SEM)	13.27 (0.29)	13.56 (0.41)		2229		.67
Handedness	% L/ R	11/ 89	6/ 94			.95	.33
Current diagnosis	*n* MDD	22	13			2.31	.13
	n ANX	22	12			2.94	.09
	n CDA	13	13			.00	1
	n HC	40	10			18.00	.00
Lifetime diagnosis	% MDD	43.29	72.92			11.31	.00
	% ANX	41.24	60.42			4.74	.03
MADRS	Mean (SEM)	7.10 (.94)	12.30 (0.16)		1428		.00
BAI	Mean (SEM)	8.79 (1.04)	11.91 (1.41)		1603		.01
Scan location	% A/ L/ G	28.9/ 41.2/ 29.9	37.5/ 39.6/ 22.9			1.34	.51
Frequency of CEM	%S/R/O/V	0	8.5/ 51.0/ 21.3/ 19,2				
Gray Matter	Mean (SEM)	740.40 (7.98)	739.73 (8.79)	.00			.96
White matter	Mean (SEM)	491.33 (6.94)	499.57 (9.57)	.47			.59

Note. CEM= Childhood Emotional Maltreatment, ANX= Anxiety Disorder, MDD= Major Depressive Disorder, CDA = Comorbid Depression and Anxiety Disorder, S=sometimes, R=regularly, O=often, V= very Often, A= Amsterdam Medical Center, L= Leiden University Medical Center, G= University Medical Center Groningen, MADRS= Montgomery Åsberg Depression Rating Scale, BAI= Beck Anxiety Inventory, F,U, X^2 = F ratio, Mann Whitney U statistic, and Chi-square test statistic, SEM= Standard Error of Mean.

SECTION 3: THE IMPACT OF CHILDHOOD EMOTIONAL MALTREATMENT ON BRAIN FUNCTIONING

Chapter 5: Enhanced Amygdala reactivity in adults reporting Childhood Emotional Maltreatment

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ABSTRACT

In the context of chronic childhood emotional maltreatment (CEM; emotional abuse and/or neglect), adequately responding to facial expressions is an important skill. Over time, however, this adaptive response may lead to a persistent vigilance for emotional facial expressions. The amygdala and the medial prefrontal cortex (mPFC) are key regions in face processing. However, the neurobiological correlates of face processing in adults reporting CEM are yet unknown. We examined amydala and mPFC reactivity to emotional faces (Angry, Fearful, Sad, Happy, Neutral) versus scrambled faces in healthy controls and unmedicated patients with depression and/or anxiety disorders reporting CEM before the age of 16 (n=60), and controls and patients who report no childhood abuse (n=75). We found that CEM is associated with enhanced bilateral amygdala reactivity to emotional facial expressions in general, independent of psychiatric status. Furthermore, we found no support for differential mPFC functioning, suggesting that amygdala hyperresponsivity to emotional facial perception in adults reporting CEM may be independent from top-down influences of the mPFC. These findings may be vital in understanding the increased emotional sensitivity, and interpersonal difficulties, that has been reported in individuals with a history of CEM.

INTRODUCTION

Childhood Emotional maltreatment (CEM) encompasses any act of commission (i.e. verbal abuse) or omission (i.e. emotional neglect) that is (potentially) harmful, or insensitive to the child's emotional development (Egeland, 2009; Gilbert et al., 2009). One in ten children growing up in Western societies experiences CEM per year (Gilbert et al. 2009), and CEM has been associated with a cascade of negative outcomes on behavioral, emotional, and social functioning (Egeland, 2009; Gilbert et al., 2009; Gibb et al., 2007; Spinhoven et al. 2010; Teicher et al. 2006). For instance, CEM is associated with enhanced emotional sensitivity in adulthood, as evidenced by enhanced negative self-associations, depressive symptoms, and difficulties in interpersonal relationships (Egeland, 2009; Gilbert et al., 2009; Spertus et al., 2003; van Harmelen et al., 2010).

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. However, over time, this adaptive response may lead to a persistent vigilance for negative facial expressions (Gibb et al., 2009). The amygdala is a key 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; Kim et al., 2011; Onur et al., 2009). In addition, adverse rearing environments in animals, such as maternal isolation, loss, or isolation rearing induce a cascade of long-term alterations on a behavioral and neurobiological level, with specific effects in the amygdala (Sanchez, 2001; McEwen et al., 2012). For instance, maternal deprivation is associated with a lasting enhancement of contextual and cued fear conditioning (Oomen et al., 2010) and anxious behaviour in rats (Eiland & McEwen, 2012).

In humans, acute stress is associated with subsequent amygdala hypervigilance to emotional stimuli (van Marle et al., 2010; Oei et al., 2012). 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), and in young adults reporting high childhood family stress (including CEM and physical abuse) while classifying the emotion of fearful and angry faces (Taylor et al., 2006). Thus far, however, it is unknown whether CEM in isolation (i.e. without comcomittant physical or sexual abuse) is related to enhanced amygdala activation for negative emotional faces. Furthermore, it is unknown whether CEM related amygdala activation persists into adulthood, i.e., whether adults reporting CEM are characterized by enhanced amygdala response to negative emotional faces.

Using functional-Magnetic Resonance Imaging (f-MRI), an emotional faces task (employing Angry, Fearful, Sad, Happy, Neutral and Scrambled faces) and applying a hypothesis driven Region of Interest (ROI) analysis approach, we examined amygdala functioning in a large sample (N = 135) of

unmedicated outpatients (with depression and/or anxiety) and healthy controls. We investigated whether patients and controls reporting CEM (n=60) showed enhanced amygdala reactivity to emotional faces compared to patients and controls reporting No Abuse (n=75). In line with Maheu et al. (2010), we expected that individuals reporting CEM showed enhanced amygdala response to negative emotional faces (i.e., Angry, Fearful and Sad), but not to happy, or neutral faces. In addition, our group recently reported reduced mPFC gray matter volume in adults reporting CEM (van Harmelen, van Tol et al., 2010). However, it is unknown whether the reduced mPFC volume in these adults reporting CEM (van Harmelen, van Tol et al., 2010) is also related to altered mPFC responsivity. Therefore, we also investigated differences between the CEM and control group with respect to mPFC reactivity to emotional faces.

In addition, to examine whether altered Amygdala and mPFC activation in response to negative emotional faces is related to psychopathology, we investigated whether abnormal amygdala (and/or mPFC functioning) was more apparent in emotionally maltreated individuals with a depression and/or anxiety disorder compared to emotionally maltreated individuals who never developed a depression and/or anxiety disorder.

METHODS

PARTICIPANTS FOR THE NESDA-MRI STUDY

Participants were drawn from the Netherlands Study of Depression and Anxiety (NESDA, N=2981). A subset of this large observational cohort study (Penninx et al., 2008), were selected to undergo Magnetic Resonance Imaging (MRI) scanning (233 patients and 68 HC). All participants underwent MRI in one of the three participating centers (i.e. Leiden University Medical Center, Academic Medical Center Amsterdam, and University Medical Center Groningen). The Ethical Review Boards of each center approved this study. After complete description of the study to the subjects, written consent was obtained.

Inclusion criteria for the NESDA-MRI patients were: current major depressive disorder (MDD) and/or anxiety disorder (AD) (panic and/or social anxiety disorder) in the last 6 months according to DSM-IV criteria. Diagnoses were established using the structured Composite International Diagnostic Interview (Wittchen et al., 1991), administered by a trained interviewer.

Exclusion criteria for patients in the NESDA-MRI study were: the presence of axis-I disorders other than MDD, panic disorder or social anxiety disorder (except generalized anxiety disorder); any use of psychotropic medication other than a stable use of Selective Serotonin Reuptake Inhibitors (SSRI) or infrequent benzodiazepine use (3×2 tablets weekly, or within 48 hrs prior to scanning), the presence of major internal or neurological disorders; dependence or past year abuse of alcohol and/or drugs; hypertension (>180/130mm Hg); heavy smoking (>5 cigarettes/day); and general MRI-

contra-indications. Controls had no lifetime depressive or anxiety disorders and were not taking any psychotropic drugs.

In the current study, some additional exclusion criteria were formulated; patients using SSRI (n=79) were excluded given its potential effect on face processing (Fu et al., 2004; Sheline et al., 2001). Moreover, we excluded 58 participants because of incomplete fMRI data (n=9), technical difficulties (n=24), or poor imaging quality (n=25). See supplement for additional information on the excluded groups.

Table 1. Clinical and demographic characteristics of participants reporting Childhood Emotional Maltreatment vs. No Abuse.

		No Abuse (n=75)	CEM (n=60)	F	X^2	P
Gender (n)	Male/Female	26/49	20/40		.03	.87
Handedness (n)	Left/Right	9/66	4/56		1.09	.30
Scan location (n)	AMC/LUMC/UMCG	16/32/27	14/28/18		.54	.76
		Mean (SE)	Mean (SE)			
Age		34.91 (1.22)	38.22 (1.32)	3.36		.07
Education		13.32 (0.34)	12.52 (0.38)	2.49		.12
Neuroticism		32.69 (1.26)	39.53 (0.93)	14.83		.00
Recent Life events		0.58 (0.11)	0.83 (0.16)	1.88		.17
Current diagnosis					8.73	.03
Major Depressive Disorder (*n*)		18	14			
Anxiety Disorder (*n*)		17	17			
Comorbid Depression and Anxiety Disorder (*n*)		11	18			
Healthy Controls (*n*)		29	11			
Lifetime diagnosis						
Major Depressive Disorder (*n*)		34	44		10.71	.001
Anxiety Disorder (*n*)		32	38		5.70	.013
Beck Anxiety Inventory		9.19 (1.22)	11.38 (1.11)	1.69		.19
Montgomery Åsberg Depression Rating Scale		7.64 (1.13)	12.88 (1.32)	9.18		.003
Concurrent abuse						
Physical abuse (n)		0	7			
Sexual abuse (n)		0	11			
Physical & sexual abuse (n)		0	5			

Note. CEM= Childhood Emotional Maltreatment, AMC= Amsterdam Medical Center, LUMC= Leiden University Medical Center, UMCG= University Medical Center Groningen.

Childhood Emotional Maltreatment was defined as emotional neglect and/or psychological abuse before the age of 16 years, as measured with the NEMESIS trauma interview (see below for more details concerning this interview). Because we did not expect that a single incident of CEM would chronically alter brain functioning, we excluded individuals reporting only a single incident of CEM (n=24). Moreover, also individuals reporting childhood physical or sexual abuse without CEM (n=5) were excluded. The final sample consisted of 135 participants (see Table 1 for all demographic and clinical characteristics). Individuals who reported emotional neglect or emotional abuse in childhood that had occurred more than once were included in the CEM group (n=60; 30 individuals reported only emotional neglect, two reported only emotional abuse, and 28 reported both emotional neglect and abuse; 59 individuals reported their biological parents as perpetrators, and one subject reported a sibling as the perpetrator). Individuals who did not report emotional, physical, and sexual maltreatment were included in the No Abuse group (n=75; Table 1).

The CEM and No Abuse groups did not differ in years of education, recent life events, anxious symptomatology, gender, handedness, or scan location (see Table 1). However, the CEM group was slightly older, had higher neuroticism scores, reported more depressive symptomatology, and consisted of more individuals with a current psychiatric diagnosis.

CHILDHOOD MALTREATMENT

Childhood maltreatment was assessed through the NEMESIS trauma interview (de Graaf et al., 2002; 2004). In this interview, respondents were asked whether they had experienced emotional neglect, emotional abuse, physical abuse, and/or sexual abuse before the age of 16, how often this had occurred (never, once, sometimes, regularly, often, or very often), and what their relationship with the perpetrator was. Emotional neglect was described as: '*people at home didn't listen to you, your problems were ignored, you felt unable to find any attention or support from the people in your house*'. Emotional abuse was described as: '*you were cursed at, unjustly punished, your brothers and sisters were favored – but no bodily harm was done*'.

Our definition of Childhood Emotional Maltreatment (i.e. emotional neglect and/or psychological abuse before the age of 16 years) is based on the American Professional Society on the Abuse of Children (APSAC; Bingelli, Hart, & Brassard, 2001; Egeland, 2009). This definition states that emotional child maltreatment consists of acts of commission (emotional abuse such as degrading, terrorizing, belittling, blaming, exploiting) and/or omission (emotional neglect e.g. isolation, rejection, denying emotional responsiveness), that conveys to the child that that he/she is worthless, unloved, and unwanted, and are harmful to the child's emotional developmental needs.

ADDITIONAL QUESTIONNAIRES

Recent life events (past year) were assessed using the List of Threatening Events Questionnaire (Brugha et al., 1985). Neuroticism was measured with the NEO Five-Factor Inventory (Costa & McGrae, 1992). Furthermore, at the day of scanning, depression and anxiety severity (past week) was measured using the Montgomery Åsberg Depression Rating Scale (Montgomery & Asberg, 1979) and Beck's Anxiety Inventory (Beck et al., 1988).

THE FACES TASK

The faces paradigm was based on the event-related emotional paradigm used by Wolfensberger and colleaugues (2008), that has been found to robustly activate the amygdala. Photographs of angry, fearful, sad, happy, neutral faces, and a control condition (scrambled faces) were presented to all participants. The photographs were selected from the Karolinska Directed Emotional Faces System (Lundqvist et al., 1998), representing standardized facial expressions of emotions expressed by amateur actors. Twenty-four stimuli were selected for each of five facial expressions,

comprising twelve female and twelve male faces. Each particular face was not presented more than four times. The scrambled faces were presented eighty times. The faces task was presented using E-prime software (Psychological Software Tools, Pittsburgh, PA, USA). In order to reduce anticipatory effects, an event-related design was employed. This entailed a pseudo-random presentation of a total of 200 stimuli against a black background. Each photograph was shown on the screen for 2.5 seconds, with an inter-stimulus (black screen) interval varying between 0.5 and 1.5 seconds. The images were projected onto a translucent screen at the end of the scanner bed, visible via a mirror above the participant's head. All participants were instructed to indicate each face's gender by pressing one of two buttons with the index finger of the left or right hand. During the presentation of scrambled faces, participants had to press left or right buttons in conformity with an arrow pointing to the left or to the right. The reaction times were recorded.

MRI ACQUISITION

Imaging data were acquired using Philips 3T MR-systems (Best, The Netherlands) located at the University Medical Centers in Leiden, Amsterdam and Groningen, equipped with a SENSE-8 (Leiden and Groningen) and a SENSE-6 (Amsterdam) channel head coil, respectively. For each subject, echo-planar images were obtained using a T2*-weighted gradient echo sequence (repetition time [TR]=2300 ms, echo time [TE]=30ms [Groningen: TE=28 ms], matrix size: 96×96 [Groningen: 64×64], 35 axial slices [Groningen: 39 slices], interleaved acquisition, 2.29×2.29 mm in-plane resolution [Groningen: 3×3mm], 3mm slice thickness). Echo-planar images were scanned parallel to the anterior-posterior commissure plane. To control for differences in scan sites, we added dummy variables for the different scan centers to all analyses. The faces paradigm was part of a functional scanning session utilizing multiple tasks, the results of other tasks are reported elsewhere.

FUNCTIONAL MAGNETIC RESONANCE IMAGING DATA PREPROCESSING

Functional imaging data were preprocessed and analyzed using Statistical Parametric Mapping (SPM)-5 software implemented in Matlab 7.1.0 (www.mathworks.co.uk). Preprocessing, after extensive quality evaluation of the data, consisted of manually reorienting the functional images to the anterior commissure, slice time correction, image realignment, registration of the T1-scan to the mean echo-planar image, warping to Montreal Neurological Institute (MNI)-space as defined by the SPM5 T1-template, reslicing to 3×3×3mm voxels and spatial smoothing using an 8mm full width half maximum Gaussian kernel. Subject movement (>3mm) resulted in exclusion of the data from further analysis.

FMRI DATA ANALYSIS

FMRI-data were analyzed in the context of the General Linear Model. Haemodynamic responses to each stimulus were modeled with a delta function convolved with a synthetic haemodynamic response function. Low-frequency noise was removed by applying a high-pass filter (cut-off 128s) to the fMRI time-series at each voxel. Statistical parametric maps for each comparison of interest were calculated on a voxel-by-voxel basis.

For each subject, contrasts for Facial expressions (Angry, Fearful, Sad, Happy, Neutral) versus scrambled faces were computed. We then conducted a Facial expressions (Angry, Fearful, Sad, Happy, Neutral) ×Group (CEM vs. No Abuse) second level analysis, to examine the main effect of task in our ROIs (i.e., amygdala and mPFC). We specified dummy variables for the different scan centers and a weighted dummy for psychiatric status as covariates. In the weighted dummy for psychiatric status (with values 0 or 0.43), the value for the patient group (n=94) was weighed according to the size of the control group (41/94=0.43). In addition, because of findings of age and gender related differences in amygdala response for emotional processing (Iidaka et al., 2002; Wager et al., 2003), we also specified age and gender as covariates. All results are reported in MNI space, and significance threshold for the main effect of task was set at $P<0.05$ Family Wise Error (FWE) corrected for multiple comparisons. To investigate if there were any CEM related activations outside our predefined ROIs, we performed a whole brain analysis with at $P<0.05$ FWE corrected.

For the amygdala, we extracted activations for the main effect of task (F) using the Marsbar ROI Toolbox, (Brett et al., 2002). The binary mask in MNI space of the left and right amygdala was specified using the Wake Forest University (WFU) Pick Atlas software, SPM Toolbox (http://fmri.wfubmc.edu).

Because the anatomical region of the mPFC is less well defined than the amygdala, group differences (F) in mPFC activations were examined using a Facial expressions (Angry, Fearful, Sad, Happy, Neutral)×CEM (CEM vs. No Abuse) voxel-wise ROI analysis, while masking for the main effect of task (F). The ROI mask (see Figure 1a) was based on the anatomical location of both dorsal and ventral mPFC (including the anterior cingulate cortex) in MNI space (using the WFU Pick Atlas toolbox). Dummy variables for the different scan centers, gender, age, and psychiatric status (weighted) were specified as covariates. Significance for group differences was set at $P<0.001$ uncorrected, with spatial extent threshold of 5 contiguous voxels.

Based on our previous findings of mPFC volume reductions in CEM in largely the same cohort (van Harmelen, van Tol et al., 2010), group differences in activation within this region were also examined by extracting mean activation differences per valence type within this locus using a binary mask that was based on our earlier findings ([x=-11 y=21 z=44]; cluster size 767; see Figure 1b, van Harmelen, van Tol et al., 2010).

Following the extraction of Amygdala and mPFC activations (using MARSBAR) we ran correlation analyses to further investigate whether average Amygdala activations for all facial expressions were related to the average mPFC activations for all facial expressions, within the No Abuse, or CEM group.

SPSS DATA ANALYSIS

Psychometric and performance data were analyzed with SPSS 17. Based on the observed distribution of the data, the appropriate parametric (F) or non-parametric Chi-square [$\chi 2$] test was performed. Because the CEM group was slightly older (Table 1), age was defined as a covariate in all SPSS analyses (however, all results remained the same when removing age as covariate). In addition, to investigate whether the results are dependent on psychiatric status, in all analyses, we added a weighted dummy for psychiatric status as a covariate. To further examine the exact impact of psychiatric status on emotional face processing in individuals reporting CEM, we finally performed an additional Diagnosis (MDD, AD, Co-morbid MDD and AD (CDA), Healthy Controls (HC))×CEM (No Abuse, CEM) Analysis of Variance.

Significance was set at $P<0.05$, two tailed, all tests were Bonferroni-corrected for multiple comparisons.

RESULTS

PERFORMANCE ON FACES TASK

Performance on faces was assessed using a Facial expressions (Angry, Fearful, Sad, Happy, Neutral)×CEM (CEM vs. No Abuse) Repeated Measures (RM) Analyses of Covariance (ANCOVA) on the reaction times. Individuals reporting CEM had similar reaction times as individuals reporting No Abuse ($F(1,130)=0.002$, $P=0.96$) and there was no CEM×Facial expressions interaction ($F(4,520)=1.03$, $P=0.39$). There was a main effect of Facial expressions ($F(4,520)=2.41$, $P=0.049$, Cohen's d (d)=0.27). Compared to the other faces, participants were faster in labeling the gender of angry faces, all P's<0.001, independent of maltreatment-status ($F(4,520)=1.03$, $P=0.39$). Moreover, age had a main effect ($F(1,130)=6.74$, $P=0.011$, $d=0.45$), with older participants having longer reaction times. Psychiatric status did not affect reaction times ($F(1,130)=0.22$, $P=0.64$).

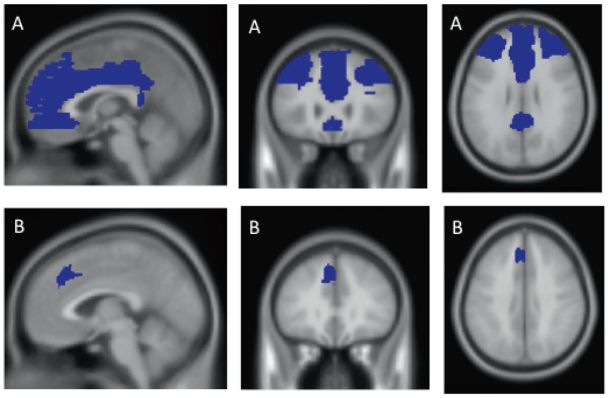
THE MAIN EFFECT OF TASK

A Facial expressions (Angry, Fearful, Sad, Happy, Neutral)×CEM (CEM vs. No Abuse) analysis showed that the task was associated with significant activations in left and right amygdala (x=-18 y=-6 z=-15, cluster size/number of voxels (K)=236, Z>8, P<0.001) & (x=18 y=-6 z=-15, K=263, Z>8, P<0.001) (Figure 2).

Furthermore, the task was also associated with significant activations in the mPFC (x=6 y=36 z=24, K =50, Z=5.52, P<0.001) & (x=9 y=48 z=-3, K =37, Z=5.04, P<0.001), all results are FWE corrected. Other regions that were

activated with task (including the right and left Fusiform Gyrus, the middle Occipital Gyrus, and the Superior Frontal Gyrus) are specified in Table 2. However, a Facial expressions (Angry, Fearful, Sad, Happy, Neutral)×CEM (CEM vs. No Abuse) whole brain analysis at P<0.05 FWE corrected, showed no CEM related activations in any of the task related regions outside our ROIs (see also Table 3).

Figure 1. ROI Masks for the mPFC.



Note. A= Cluster based on anatomical regions of the dorsal mPFC, ventral mPFC and entire ACC. B= Cluster based on structural differences in CEM groups as reported in Van Harmelen, van Tol al., 2010.

Figure 2. Amygdala activation for the main effect of task (emotional versus scrambled faces).

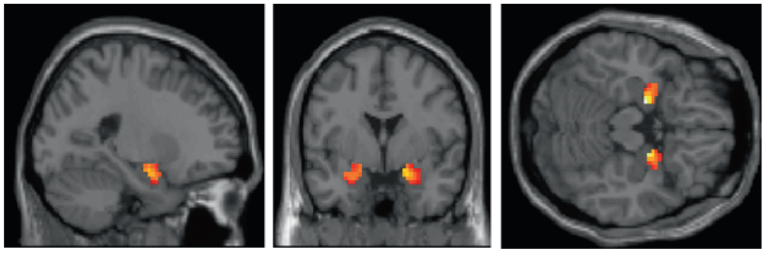


Table 2. Significant gray matter clusters of the main effect of task (F) at P <.05 Family Wise Error corrected

	K	F	Z	P	x,y,z
Right Fusiform Gyrus	271	411.86	>8	<.001	42 -51 -21
		145.76	>8	<.001	42 -78 -12
		101.69	>8	<.001	24 -93 -9
Left Fusiform Gyrus	115	200.84	>8	<.001	-39 -51 -21
Left Middle Occipital Gyrus	3555	198.59	>8	<.001	-27 -90 9
		186.01	>8	<.001	30 -87 12
		155.74	>8	<.001	-24 -69 -15
Right Amygdala	263	175.88	>8	<.001	18 -6 -15
		77.15	>8	<.001	27 3 -21
Left Amygdala	236	167.89	>8	<.001	-18 -6 -15
		29.29	5.22	<.001	-39 15 -24
Right Superior Frontal Gyrus	350	75.37	>8	<.001	48 24 24
		74.11	>8	<.001	51 30 18
		64.59	7.75	<.001	45 9 30
Left Superior Frontal Gyrus	83	55.29	7.19	<.001	-27 60 9
Right Superior Parietal Lobe	149	53.2	7.05	<.001	54 -48 39
Left Superior Parietal Lobe	375	52.05	6.98	<.001	-51 -48 42
		50.92	6.9	<.001	-45 -48 48
		45.93	6.56	<.001	-60 -39 36
Right Superior Temporal Gyrus	117	44.1	6.43	<.001	66 -21 9
		26.33	4.95	<.001	63 -21 -6
		23.5	4.66	<.001	57 -27 18
Right Superior Frontal Gyrus	11	33.22	5.57	<.001	24 15 54
Right Anterior Cingulate Cortex	54	32.65	5.52	<.001	6 36 24
Right Superior Frontal Gyrus	51	32.33	5.49	<.001	30 54 21
		28.5	5.15	<.001	21 63 6
Right Medial Frontal Gyrus	37	27.36	5.04	<.001	9 48 -3
		26.27	4.94	<.001	3 48 6

Table 3. Significant CEM related gray matter activations outside our ROIs.

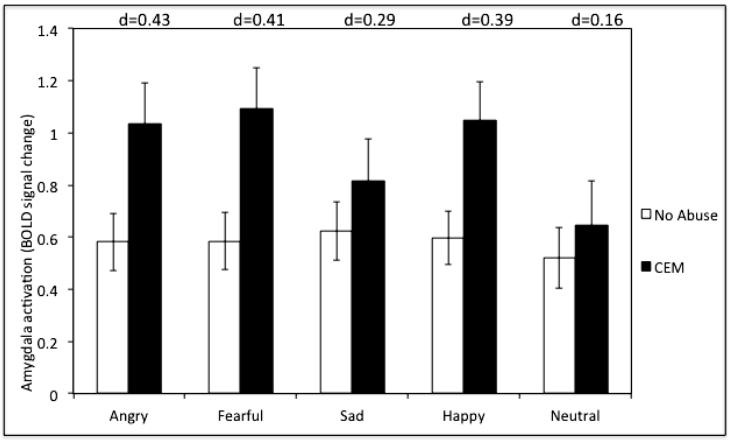
	K	F	Z	P	x,y,z
Left Middle Temporal Gyrus	35	19.52	4.23	<.001	54 -60 -3
Left Lingual Gyrus	21	17.64	4.01	<.001	18 -72 -15
Right Middle Temporal Gyrus	5	14.51	3.61	<.001	36 -81 21
Right Superior Temporal Gyrus	14	13.77	3.51	<.001	51 -30 15
		11.44	3.17	<.001	48 -36 21
Right Lingual Gyrus	9	12.58	3.34	<.001	21 -72 -12
Left Postcentral Gyrus	8	12.55	3.34	<.001	-57 -27 18

Note. Main effect of CEM vs No Abuse (F) whole brain at P<.001, uncorrected, with spatial extent threshold of 5 contiguous voxels.

AMYGDALA ACTIVATION IN RESPONSE TO EMOTIONAL FACES

We next extracted bilateral amygdala activations for the main effect of task (F), and conducted a Facial expressions (Angry, Fearful, Sad, Happy, Neutral)×Lateralization (left amygdala vs. right amygdala) RM ANCOVA with CEM (CEM vs. No Abuse) as fixed factor. Lateralization was added as fixed factor to investigate a possible effect of lateralization (see Maheu et al 2010). In line with our expectations, individuals reporting CEM showed enhanced amygdala activation compared to the No Abuse group (F(1,131)=5.96, P=0.016, d=0.43, see Figure 3).

Figure 3. Estimated marginal means and standard errors of mean amygdala activation in individuals reporting No Abuse vs. Childhood Emotional Maltreatment (CEM).



Note. d= Cohens d for the difference between amygdala activation within the No Abuse versus CEM group.

There was no main effect of Facial expressions (F(4,524)=0.354, P=0.83), nor Lateralization (F(1,131)=0.22, P=0.64). Moreover, CEM did not interact with Facial expressions (F(4,524)=0.89, P=0.47, Lateralization (F(1,131)=1.25, P=0.26), or Facial expressions×Lateralization (F(4,524)=0.89, P=0.47). Finally, age and psychiatric status did not have a main effect on amygdala activation (F(1,131)=1.45, P=0.23) & F(1,131)=2.22, P=0.14). Also when performing a Diagnosis (MDD, AD, CDA, HC)×CEM (No Abuse, CEM) analysis, with Age as covariate, all results remained unchanged, including the main effect of CEM (F(1,126)=5.26, P=0.02). Moreover, again, diagnosis did not have a main effect on amygdala activation (F(3,126)=1.28, P=0.29) nor did diagnosis interact with CEM (F(3,126)=0.22, P=0.89). This absence of a main effect of diagnosis is in line with a recent study in the larger NESDA-MRI sample, were no impact of psychopathology was found on amygdala functioning to emotional and neutral faces (Demenescu et al., 2011).

The CEM group had slightly higher neuroticism, and depression severity scores (Table 1). To investigate whether this could potentially explain our findings, we performed two additional RM ANCOVAs. When we added neuroticism as covariate to the analysis, all results remained unchanged (i.e. main effect of CEM ($F(1,130)=5.98$, $P=0.02$, $d=0.43$)). Neuroticism had no main effect ($F(1,130)=0.23$, $P=0.72$), indicating that the findings cannot be explained by the slightly higher neuroticism scores in the CEM group. Also, when we added severity of depression (as measured with the MADRS) as covariate to the analysis, all results remained unchanged (i.e. main effect of CEM ($F(1,130)=5.18$, $P=0.02$, $d=0.40$)), and depression severity had no main effect ($F(1,130)=1.04$, $P=0.31$), indicating that the findings cannot be explained by higher depression levels in the CEM group. In addition, in both the CEM and No Abuse groups,

Correlation analyses showed no significant relationships between amygdala activations to the emotional and neutral faces and Neuroticism (all P's>0.15), nor depression (all P's>0.29).

To exclude the possibility that enhanced amygdala reactivity is driven by a concurrent history of physical and/or sexual abuse in some of the participants (n=23), we next re-ran the RM ANCOVA while excluding these individuals. In this analysis, all results remained unchanged, including the main effect of CEM ($F(1,108)=5.05$, $P=0.03$, $d=0.39$).

Medial prefrontal cortex (mPFC) activation in response to emotional faces

A CEM vs. No abuse (F) ROI analysis (Figure 1a) revealed no significant CEM related activations in the mPFC (ventral and dorsal), nor in the entire ACC. These results remained unchanged when mPFC volume was added as a covariate (van Harmelen, van Tol et al., 2010). Additionally, when we extracted mPFC activations in the mPFC mask that is based on our previous findings (Figure 1b; van Harmelen, van Tol, et al., 2010), a RM ANCOVA showed that CEM did not have a main effect on activation in this region either ($F(1,131)=0.01$, $P=0.91$). Thus, individuals reporting CEM did not differ in mPFC activation in response to emotional facial expressions when compared to individuals reporting No Abuse. Also when performing a Diagnosis (MDD, AD, CDA, HC)×CEM (No Abuse, CEM) analysis, with Age as covariate, all results remained unchanged, including that CEM and diagnosis had no main effect on mPFC activation ($F(1,126)=0.001$, $P=0.98$) & $F(3,126)=1.44$, $P=0.24$), nor was there a CEM×Diagnosis interaction ($F(3,126)=1.29$, $P=0.28$). In addition, no interactions with Facial expressions were found.

Correlation between Amygdala mPFC activations

Following the extraction of Amygdala and mPFC activations (using MARSBAR) we ran correlation analyses to further investigate whether average Amygdala activations for all facial expressions were related to the average mPFC (Figure 1a) activations for all facial expressions, within the No

Abuse, or CEM group. However, the test yielded no significant relationship between amygdala and mPFC activations in the No abuse group (r=0.01, P=0.92) nor in the CEM group (r=0.01, P=0.92). Moreover, a correlational analysis with average amygdala and mPFC activations based on the cluster that we described in van Harmelen, van Tol et al. (2010) (Figure 1b) also yielded no significant relationship in the No abuse (r=0.06, P=0.59), nor the CEM group (r=0.14, P=0.29).

DISCUSSION

This is the first study to show that adults reporting CEM show enhanced amygdala activation in response to emotional facial expressions, independent of psychiatric status, neuroticism, depression severity, and history of concurrent physical or sexual abuse. The amygdala plays a key role in detecting the (emotional or biological) salience of stimuli (Kim et al., 2011; Sergerie et al., 2008; Todd & Anderson, 2009; van Wingen et al., 2011), and in enhancing levels of attention and vigilance towards these stimuli (Davis & Whalen, 2001). Therefore, our results suggest amygdalar hypervigilance towards emotional facial expressions in adults reporting CEM. Moreover, together with similar findings in a small sample of adolescents reporting severe neglect (Maheu et al. 2010), our findings suggest sustained hypervigilance even more than 20 years after the maltreatment took place.

Contrary to our hypothesis, hyperactivation of the amygdala in adults reporting CEM was not restricted to negative facial expressions, but was also found in response to happy and neutral faces, although it should be noted that the effect sizes for the neutral faces are relatively small. Therefore, amygdalar hypervigilance to facial expressions in general might indicate that individuals with a history of CEM interpret all facial expressions as highly salient. In line with this idea, neglected children are reported to have poor valence discriminatory abilities for different facial emotions (Pollak et al., 2000; Fries & Pollak, 2004; Vorria et al., 2006), and it has been suggested that neglected children may misinterpret all emotional faces as threatening (Pollak et al., 2000). In that respect, happy faces might be interpreted as a mask for more malevolent emotions (Pollak et al., 2000), for example as being laughed at. Enhanced amygdala activation in response to happy faces could also be indicative of an increased sensitivity towards positive emotional expressions in others (e.g., happy faces might function as safety signal). To disentangle the impact of negative versus positive and neutral faces in individuals reporting CEM, future studies are needed that also asses the subjective ratings of emotional faces besides amygdala activation.

On a neurobiological level, enhanced amygdala responses to all facial expressions may reflect a general noradrenergic sensitization in response to emotional stimuli in individuals reporting CEM. Chronic stress is associated with increased firing of noradrenergic neurons in the brainstem, and augmented release of noradrenalin in the brain following subsequent

stressors (Bremner, Krystal, Southwick & Charney, 1996; Elzinga & Bremner, 2002). Furthermore, enhanced amygdala activation during stress strengthens emotional memory traces and increases fear conditioning (Onur et al., 2009; Joëls & Baram, 2009; Strange & Dolan, 2004). In accordance, in rats, maternal deprivation is associated with a lasting enhancement of contextual and cued fear conditioning (Oomen et al., 2010) and anxious behaviour (Eiland & McEwen, 2012).

Another noteworthy result of this study was that enhanced amygdala reactivity to emotional faces in individuals reporting CEM was observed independent of psychiatric status and that no main effect of diagnosis was observed. This finding is in contrast with other studies finding amygdala hyperreactivity in depressed (Sheline, et al., 2001; Anand et al., 2005; Fales et al., 2008) and anxious patients (Bishop, 2007; Straube, 2004). It should be noted that our patient sample can be characterized as having relatively mild symptoms, due to the fact that we excluded patients using SSRIs. Possibly, this may have lead to an underestimation of the true effect of psychopathology. However, in a larger sample of the same cohort, in which medicated patients were also included, we recently reported no effect of psychiatric status on amygdala reactivity to emotional faces (Demenescu et al., 2011; see for similar findings; Lawrence et al., 2004; Gotlib et al., 2005; Lee et al., 2008; Almeida et al., 2009; Norbury et al., 2009, and a meta-analysis showing no amygdala hyperresponse in depressed patients; Diekhof et al., 2008). Our findings suggest that enhanced amygdala reactivity to emotional faces does not seem to be directly linked to the development of psychopathology in individuals with CEM. Apparently, additional risk factors such as genetic make-up, in itself, or in interaction with exposure to stressful life events during adulthood, or low social support additionally determine who will subsequently develop a depressive and/or anxiety disorder (Hariri et al., 2002; Kilpatrick et al., 2007).

We did not find support for abnormal mPFC functioning in individuals reporting CEM, nor did we find a significant relationship between Amygdala and mPFC activity. Thus smaller mPFC volume (van Harmelen, van Tol et al., 2010) is not related to abnormal mPFC reactivity to emotional facial expressions in adults reporting CEM. Hence, our findings suggests that amygdala hyperresponsivity to emotional facial expressions in individuals with CEM histories may occur independent of the regulatory influences of the mPFC (Fonzo et al., 2000), at least in this gender labeling task which requires minimal cognitive resources (Reddy et al., 2004). However, abnormal mPFC functioning may be observed in tasks posing greater cognitive demands (see for example Shin et al., 2006).

This study is not without its limitations. First, although a clinically diagnosed PTSD diagnosis was an exclusion criterion, unidentified current or lifetime PTSD symptoms may still have been present in the current sample, which may have influenced our findings. This is not very likely, however, given that the enhanced amygdala responses in individuals reporting CEM was unrelated to psychiatric status. Second, history of

childhood maltreatment was retrospectively assessed. In addition, it is important to acknowledge the inherent subjectivity of self-reported CEM. However, it should be noted that, in the current study, neuroticism did not explain enhanced amygdala activation, and in the overall 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 in the current sample was not critically affected by current mood state. Furthermore, a recent study showed that 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). Finally, our findings are based on a cross-sectional design; therefore, one cannot assume causality. It might be that individuals who have strong amygdala reactions to emotional faces may also have experienced certain behaviors of their parents as more abusive or neglectful. Alternatively, enhanced amygdala reactivity to emotional facial expressions may have been pre-existent and inherited by their parents, whose enhanced amygdala reactivity to emotional faces may have increased their risk to emotionally maltreat their children. Theoretically, longitudinal studies are needed to shed more light on the etiology of our findings, although from an ethical point of view, this is problematic. However, recently, a prospective study in soldiers showed that combat stress exposure is associated with enhanced amygdala responsivity to emotional faces, indicative of a causal role of stress exposure on amygdale hypervigilance. In addition, it appeared that the subjective appraisal of threat, and not the actual exposure, played a key role in amygdala regulation in the aftermath of severe stress (van Wingen et al., 2011).

CONCLUSION

We found that adults reporting CEM show enhanced amygdala response to emotional facial expressions. These findings may represent a persistent hypervigilance for emotional facial expressions in adults reporting CEM. Potentially, during social emotional encounters, enhanced amygdala activation in individuals with CEM might result in strong memory traces and increased fear conditioning in response to emotionally significant stimuli (in this case emotional facial expressions). This may be an important key in understanding the increased emotional sensitivity and difficulties in interpersonal relationships (Egeland 2009; Gilbert et al., 2009; Spertus et al., 2003; Teicher et al., 2006; van Harmelen et al., 2010) that has been reported in these individuals.

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SUPPLEMENT

EXCLUSION ANALYSES.

To investigate whether the excluded groups differed systematically on clinical characteristics from our final sample (N=135), we conducted several follow-up analyses of variance, and Chi-square tests. In line with the idea of more severe symptomatology amongst individuals using antidepressants, we found that the SSRI-users had higher neuroticism scores (Mean neuroticism score =41.95 $\pm$ 6.65) than the final sample (Mean neuroticism score =35.73 $\pm$ 10.77) ($F(1, 212)=21.49$, $p>0.001$). The SSRI-users had more anxious symptomatology (Mean anxious symptomatology =14.65 $\pm$ 8.99) than the final sample (Mean anxious symptomatology =10.16 $\pm$ 9.76) ($F(1, 210)=10.96$, $P<0.001$). Furthermore, the SSRI-users had more depressive symptomatology (Mean depressive symptomatology =16.15 $\pm$ 9.15) than the final sample (Mean depressive symptomatology =9.97 $\pm$ 10.29) ($F(1, 212)=19.48$, $P<0.001$). In line, the SSRI-users had more often a psychiatric diagnosis ($X^2=.36.59$, $df=3$, $P<0.001$).

With regard to the group of individuals that were excluded because of incomplete fMRI data (n=9), technical difficulties (n=24), or poor imaging quality (n=25), they did not differ from the final sample with regard to anxious symptomatology ($F(1,178)=1.09$, $P=0.29$), neuroticism score ($F(1, 191)=0.15$, $P=0.70$) depressive symptomatology ($F(1, 182)=1.48$, $P=0.22$), nor in number of current psychiatric diagnosis ($X^2=0.07$,$df=3$, $P=0.86$).

Finally, the group of individuals (n=29) that were excluded because they reported only a single incident of emotional maltreatment (n=24), or childhood physical or sexual abuse without CEM (n=5) did not differ from the final sample (n=135) in: anxious symptomatology ($F(1,158)=0.89$, $P=0.35$), neuroticism score ($F(1,162)=0.25$, $P=0.62$), age ($F(1,158)=0.034$, $P=0.85$), depressive symptomatology ($F(1,158)=0.09$, $P=0.77$), and current psychiatric diagnosis ($X^2=1.94$,$df=3$, $P=0.58$).

Chapter 6: Hypoactive medial prefrontal cortex activity in adults reporting childhood emotional maltreatment

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ABSTRACT

Childhood Emotional Maltreatment (CEM) has adverse effects on medial prefrontal cortex (mPFC) morphology, a structure that is crucial for cognitive functioning and (emotional) memory, and which modulates the limbic system. In addition, CEM has been linked to amygdala hyperactivity during emotional face processing. However, no study has yet investigated the functional neural correlates of neutral and emotional memory in adults reporting CEM. Using fMRI, we investigated CEM-related differential activations in mPFC during the encoding and recognition of positive, negative, and neutral words. The 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). We found a consistent pattern of mPFC hypoactivation during encoding and recognition of positive, negative, and neutral words in individuals reporting CEM. These results were not explained by psychopathology or severity of depression or anxiety symptoms, nor by gender, level of neuroticism, parental psychopathology, negative life events, antidepressant use, or decreased mPFC volume in the CEM group. These findings indicate mPFC hypoactivity in individuals reporting CEM during emotional and neutral memory encoding and recognition. Our findings suggest that CEM may increase individuals' risk to the development of psychopathology on differential levels of processing in the brain; blunted mPFC activation during higher order processing and enhanced amygdala activation during automatic/lower order emotion processing. These findings are vital in understanding the long-term consequences of CEM.

INTRODUCTION

Childhood emotional maltreatment (CEM; emotional abuse and/or emotional neglect) is experienced by one out of ten children growing up in western societies every year (Gilbert, Widom, et al., 2009). CEM is the most prevalent type of child-maltreatment and has a profound negative impact on social, cognitive, behavioral and emotional functioning (Egeland, 2009; Gilbert, Widom, et al., 2009; Hart & Rubia, 2012; Pollak et al., 2008; Schechter, 2012; Spinhoven et al., 2010). After chronic exposure to CEM, individuals may develop sustained negative self-associations (Van Harmelen et al., 2010), which may bias attention towards negative information about the self and others. Even as adults, this may result in negative interpretations when engaged in stressful interpersonal situations, or when retrieving memories of such situations (Beck, 2008). In line, individuals with CEM are more prone to develop depressive and anxiety disorders (Iffland et al., 2012; Spinhoven et al., 2010).

Chronic childhood stress is associated with structural and functional changes in the brain, especially within the (medial) prefrontal cortex [(m)PFC], hippocampus, and the amygdala (see overviews and mechanisms; (Arnsten, 2009; Danese & McEwen, 2012; Hart & Rubia, 2012; Lupien et al., 2009; McCrory et al., 2012; McEwen et al., 2012). In line, we reported CEM related smaller mPFC volume (Van Harmelen, Van Tol, et al., 2010), and amygdala hyperactivation during the processing of emotional faces in patients and healthy controls (HC) (Van Harmelen et al., 2012); see also (Bogdan, Ph, Williamson, & Hariri, 2012; Dannlowski, Kugel, et al., in press; Dannlowski, Stuhrmann, et al., 2012; McCrory et al., 2011). The mPFC is crucial for emotional -processing, -memory, and modulates the stress response (Cardinal et al., 2002; Etkin et al., 2011; Phillips et al., 2003). The dorsal mPFC plays a vital role in the (re-) appraisal of emotional stimuli, while the ventral mPFC dampens fear responses through its regulation of the amygdala (Etkin et al., 2011; Phillips et al., 2003). The dorsal and ventral mPFC are functionally inextricably intertwined, therefore abnormalities in either or both may be associated with abnormalities in emotional processing, memory, and stress response (Etkin et al., 2011; Phillips et al., 2003). The mPFC is also crucial for understanding other people's beliefs, feelings, and motivations (i.e. mentalizing) (Denny et al., 2012; Frith & Frith, 2006; Frith & Frith, 2003; Meyer et al., 2012; Mitchell, Macrae, & Banaji, 2006). In children, a smaller PFC volume has been found to mediate the link between childhood stress and reduced cognitive functioning (Hanson et al., 2012). However, the neural correlates of cognitive functioning in adults reporting CEM are unknown.

During and immediately after acute interpersonal stress, brain activity shifts from higher cortical (e.g., mPFC) regions to 'lower' subcortical regions (e.g., amygdala, hippocampus) (Hermans et al., 2011; Oei et al., 2012). Stress activates the amygdala as part of a 'salience network' for vigilant attentional reorienting, strengthening of emotional memory traces, and autonomic-neuroendocrine control, facilitating the processing/encoding of emotional

information, at the detriment of higher order cognitive functions (Davis & Whalen, 2001; Hermans et al., 2011; Oei et al., 2012; Todd, Evans, Morris, Lewis, & Taylor, 2011; Whalen, 2007). In HCs, exposure to acute psychosocial stress increases coupling of mPFC and amygdala activations, which persists even some time after the stress has waned (Veer et al., 2011). To investigate whether CEM is related to a reduction in higher order cognitive functioning, the functional neural correlates of CEM during cognitive tasks that are known to engage frontal regions need be examined.

Here, we examined the neural correlates of CEM during the encoding and recognition of (positive, negative, and neutral) words in a large sample (N=194), by comparing patients and HC reporting CEM [n=96; i.e. patients with Major Depressive Disorder (MDD; n=20), Anxiety Disorder (ANX; n=27), Comorbid Depression and Anxiety disorder (CDA; n=40), and HC; n=9)], with those reporting No Abuse [n=98; (i.e. MDD (n=24), ANX (n=22), CDA (n=19), and HC (n=33)]. We expected that self-reported CEM was associated with a memory bias (i.e. relative enhanced recognition) with respect to negative stimuli, and limbic (amygdala and hippocampal) hyperactivations during encoding and recognition of negative words, but not for positive or neutral words. In addition, we expected a general reduction in cognitive functioning in individuals with CEM, associated with overall reduced mPFC activations (across valence).

METHOD

PARTICIPANTS

Participants were a subset from the Netherlands Study of Depression and Anxiety (NESDA; N=2981; (Penninx et al., 2008)), consisting of 233 patients with MDD and/or ANX, and 68 HC. Participants underwent MRI scanning in the Leiden University Medical Center (LUMC), Academic Medical Center Amsterdam (AMC), or University Medical Center Groningen (UMCG). Trained interviewers established diagnoses using the structured Composite International Diagnostic Interview (Wittchen et al., 1991). Patients were included when they had a diagnosis <6 months recency) of current DSM-IV MDD and/or ANX (panic disorder and/or social anxiety disorder). Patients were excluded if they were taking any psychotropic medication other than stable use of selective serotonin reuptake inhibitors (SSRIs) or infrequent benzodiazepine use (i.e. equivalent to 2 doses of 10 mg of oxazepam 3 times per week or use within 48 hrs prior to scanning). HCs had no lifetime MDD or ANX, and were not taking any psychotropic drugs. Ethical Review Boards of each participating center approved this study, and after complete description of the study, written informed consent was obtained.

Childhood Maltreatment

Childhood maltreatment was assessed through the NEMESIS trauma interview (De Graaf, Bijl, Smit, Vollebergh, & Spijker, 2002), Participants were asked whether they had experienced emotional neglect, emotional abuse, physical abuse, or sexual abuse before the age of 16, and if so, how often it occurred ('*never, once, sometimes, regularly, often, or very often'*), and what their relationship with the perpetrator was. Emotional neglect was described as: '*people at home didn't listen to you, your problems were ignored, and you felt unable to find any attention or support from the people in your house'*. Emotional abuse was described as: '*you were cursed at, unjustly punished, your brothers and sisters were favored – but no bodily harm was done'*. CEM was defined as multiple incidents (>once) of emotional neglect and/or emotional abuse (In line with our previous studies e.g. van Harmelen, van Tol et al., 2010, van Harmelen et al., 2013). In the final sample (N=194, Table 1; additional exclusion criteria in supplement), 96 adults reported CEM (n=20 MDD, n=27 ANX, n=40 CDA, n=9 HC), and 98 reported No Abuse (n=24 MDD, n=22 ANX, n=19 CDA, n=33 HC). This is largely the same cohort in whom we found CEM related reduced mPFC volume (Van Harmelen, Van Tol, et al., 2010), and enhanced amygdala responses (Van Harmelen et al., 2013). In the CEM group, participants reported isolated emotional neglect (n=46, 47.9%), isolated emotional abuse (n=3, 3.1%), or both emotional neglect and emotional abuse n=47, 49.0%) in childhood. In addition, 95 participants (99.0%) reported their biological parents as perpetrators, one person (1.0%) reported a stepfather as perpetrator.

Additional assessments

In the NESDA study, we assessed lifetime negative life events with the List of Threatening Events Questionnaire (Brugha; Bebbington, Tennant, & Hurry, 1985), and Neuroticism with the NEO Five-Factor Inventory (Costa & McGrae, 1992). Parental psychopathology was assessed using a family tree approach interview, assessing whether a member of their family had experienced anxiety, depression or other psychopathological problems, and if so, which member of their family. At the day of scanning (Approx. 8 weeks following NESDA baseline assessment), severity of depression and anxiety (last two weeks) was assessed using the Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988) and the Montgomery Åsberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979).

Task paradigm

The word-encoding and -recognition task was event-related, subject-paced (max 5s) (Daselaar, Veltman, Rombouts, Raaijmakers, & Jonker, 2003), supplement). During encoding, participants were asked to classify 40 positive, 40 negative, and 40 neutral words according to their valence. During a baseline control condition, participants viewed the words 'left', 'middle', or 'right' and were instructed to press the corresponding key. After a ten minute retention interval, participants indicated whether they had

'seen' (i.e. remembered), 'probably had seen' (i.e. know), or 'hadn't seen' (i.e. rejection) 120 old encoding target words, 120 new distracter words, and 40 baseline control trials. Trial presentation was pseudo-randomized. We recorded response accuracy and times (RT). Anxiety levels were recorded before and after word encoding and recognition using a Visual Analogue Scale (0-100; Huskisson, 1993).

Table 1. Clinical and demographic characteristics of the CEM vs. No Abuse groups.

	No Abuse (N=98)		**CEM (N=96)**				
	Mean	SD	Mean	SD	χ^2	F	P
Age	36.48	10.56	38.11	9.52		1.28	0.26
Gender (male/female)(n)	32/66		37/59		.73		0.39
Education level (attained in years)	13.16	2.88	12.5	3.28		2.24	0.14
Scan location (A/L/G)(n)	30/37/31		32/38/26		.50		0.78
Diagnosis (yes/no) (n)	65/33		87/9		16.88		<.001
Diagnosis (MDD/CDA/ANX/HC) (n)	24/19/22/33		20/40/27/9		22.04		<.001
Type of abuse (CEM+S / CEM+P/ CEM+S&P) (n)			56/16/13/11				
Frequency of CEM (Som/Reg/Often/very Often) (n)			15/27/19/35				
SSRI use (yes/no) (n)	21/77		29/67		1.95		0.16
Parental Psychopathology (yes/no) (n)	38/25		54/18		3.37		0.07
Negative Life events	4.06	1.97	5.43	2.17		20.99	<.001
Neuroticism	34.31	7.93	41.81	9.34		36.31	<.001
MADRS	8.19	9.29	15.08	9.99		26.81	<.001
BAI	9.29	9.62	12.82	9.04		6.63	<.011
Anxiety score (VAS) before encoding	34.12	24.71	34.94	27.27		0.05	0.83
Anxiety score (VAS) after encoding	29.54	21.66	30.13	24.75		0.03	0.86
Word classification							
Proportion words classified as positive	98.94	24.04	98.37	22.35		0.03	0.87
Proportion words classified as negative	96.97	5.68	96.07	11.39		0.45	0.51
Proportion words classified as neutral	103.14	24.52	102.77	25.03		0.01	0.92
Memory							
Proportion correctly recognized positive words	0.73	0.13	0.73	0.15		0.01	0.93
Proportion correctly recognized negative words	0.69	0.13	0.69	0.16		0.07	0.80
Proportion correctly recognized neutral words	0.69	0.15	0.71	0.17		1.41	0.24
Proportion false alarms positive words	0.12	0.10	0.11	0.09		0.03	0.85
Proportion false alarms negative words	0.17	0.11	0.15	0.10		1.27	0.26
Proportion false alarms neutral words	0.06	0.06	0.06	0.05		0.00	0.97
Discriminant sensitivity positive words	0.61	0.16	0.62	0.15		0.04	0.85
Discriminant sensitivity negative words	0.52	0.12	0.54	0.14		1.40	0.24
Discriminant sensitivity neutral words	0.63	0.16	0.65	0.17		1.37	0.24

Note. A= Amsterdam, L= Leiden, G=Groningen, S= Sexual abuse, P= Physical abuse, Som= Sometimes, R= Regularly, Discriminant sensitivity= proportion correctly recognized words- proportion false alarms

IMAGE ACQUISITION

Imaging data were acquired using Philips 3-Tesla MRI-systems (Best, The Netherlands) located at the LUMC, AMC, and UMCG, equipped with SENSE-8 (LUMC, UMCG) and SENSE-6 (AMC) channel head coils. Echo-planar images were obtained using a T2*-weighted gradient echo sequence (repetition time [TR]=2300ms; echo time [TE]=30ms [UMCG: 28 ms], matrix size: 96×96 [UMCG: 64×64], 35 axial slices [UMCG: 39], interleaved acquisition, 2.29×2.29mm in-plane resolution [UMCG: 3×3mm], 3mm slice thickness). Anatomical imaging included a sagittal 3-dimensional gradient-echo T1-weighted sequence (TR=9ms, TE=3.5ms; matrix 256×256; voxel size: 1×1×1mm; 170 slices).

IMAGING DATA

Functional imaging data were preprocessed in Statistical Parametric Mapping software (SPM5) in Matlab7.1 (www.mathworks.co.uk), and analyzed using SPM8 in Matlab7.8. Preprocessing of the imaging data included reorientation of the functional images to the anterior commissure, slice time correction, image realignment, registration of the T1-scan to the mean image, warping to Montreal Neurological Institute (MNI)-space as defined by the SPM5 T1-template, reslicing to 3×3×3mm voxels and spatial smoothing using an 8-mm FWHM Gaussian kernel. Next, data were analyzed in the context of the General Linear Model. Haemodynamic responses to each stimulus were modeled with a delta function convolved with a synthetic haemodynamic response function and modulated using RT. The model included regressors for encoding[VI] and recognition[VII] parameters. In addition, filler words, error- and no-response trials were included as a regressor of no interest. Low-frequency noise was removed by applying a high-pass filter (cut-off: 128s) to the fMRI time-series at each voxel. Owing to the small proportion of 'know responses' on the recognition trials, these responses were treated as 'remembered' and added to either correct recognition (CREC) or false alarms (FA).

Contrast images for subsequently correctly recognized (SCR) words during encoding (SCR_pos>baseline, SCR_neg>baseline, SCR_neu>baseline), and CREC words during recognition (CREC_pos>baseline, CREC_neg>baseline, and CREC_neu>baseline) were calculated per subject on a voxel-by-voxel basis and entered into second-level analyses for between-group comparisons.

We next set up CEM (No Abuse, CEM)×Words (Positive, Negative, Neutral) RM ANCOVAs for the encoding and recognition task separately. Age, gender and education level were specified as covariates (Hart & Rubia, 2012; Iidaka et al., 2002), and two dummy variables were added as covariates to control for variation caused by the different scanning locations. To examine if CEM related word encoding and recognition was confounded by individual's psychiatric status, we also added a dummy for current MDD, ANX (yes/no), demeaned within the CEM and No abuse group to control for variation caused by psychopathology. Because only 9 HC reported CEM, we were unable to perform group (MDD, ANX, CDA, HC)×CEM (No Abuse, CEM) RMANOVAs, as these analyses would be seriously underpowered. For the specific effects of MDD, ANX, and HC on word encoding and recognition in largely the same sample see van Tol et al. (2012).

We defined the following ROIs: hippocampus, amygdala, and mPFC. Because the anatomical location of the mPFC is less well defined than that of

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[VI] *SCR_pos, SCR_neg, SCR_neu, SMISS_pos, SMISS_neg, SMISS_neu, BL. (SCR=subsequently correct; SMISS=subsequently missed)*

[VII] *CREC_pos, CREC_neg, CREC_neu, CREJ_pos, CREJ_neg, CREJ_neu, FA_pos, FA_neg, FA_neu, MISS_pos, BL. (CREC=Correct recognition; CREJ=correct rejections; MISS=misses).*

the hippocampus and amygdala, we focused on the mPFC in the broadest sense (i.e. dorsal mPFC (Brodmann area (BA) 8 and 9), ventral mPFC (BA 10), dorsolateral mPFC (BA 8, 9, and 46), and the dorsal and pregenual ACC (BA 32,24), using the AAL toolbox implemented in the Wake Forest University (WFU)-Pickatlas (Maldjian, Laurienti, Kraft, & Burdette, 2003). The main effects of task are reported at P<.05, Family Wise Error (FWE) (voxel level). Activations outside our ROIs were examined using whole-brain analyses at P<.05 FWE corrected, while masking for the main effect of task (P<.05 uncorrected). All results are reported in MNI space.

Bilateral Amygdala (131 voxels) and hippocampal (536 voxels) activations were examined by extracting their activations for the main effect of task (F) to SPSS using Marsbar (Brett, Valabregue, & Poline, 2002), and binary masks using WFU-Pickatlas. MPFC activations were examined using CEM vs. No Abuse (F) analysis at P<0.005, uncorrected, and post-hoc t-tests had to meet P<.05 FWE corrected for the spatial extend of the activated region with an initial height threshold of Z>3.09, and K>5 voxels, while masking for the main effect of task (P<.05 uncorrected). For this small volume correction (P_{SVC}) we used the WFU-pickatlas, and to extract significant mPFC activations to SPSS we used the Marsbar Toolbox.

BEHAVIORAL ANALYSES

Psychometric and performance data were analyzed with SPSS-19. Proportions (p) Correctly Recognized words (pCREC), False Alarms (pFA), and old/new discriminant accuracy (d'=pCREC-pFA) were calculated for positive, negative, and neutral words. For all tests, significance was set at P<.05 two-tailed, Bonferroni-corrected.

RESULTS

CEM VS NO ABUSE GROUP CHARACTERISTICS AND MEMORY PERFORMANCE.

The CEM vs No Abuse groups did not differ in age, education, gender, SSRI-use, scan location, and anxiety levels before and after the task. The CEM group included more patients, reported higher depressive and anxious symptomatology, higher neuroticism scores, more lifetime negative life events, and slightly more parental psychopathology (Table 1). RM ANOVAs revealed no differences in valence classification[VIII], memory performance, nor RTs, between the CEM and No Abuse groups (Tables 1 & S1).

IMAGING RESULTS

MAIN EFFECT OF TASK DURING WORD ENCODING.

The main effect of task during encoding was associated with bilateral amygdala (K=6, x=-18, y=-6, z=-18, Z-score (Z)= 6.72) & (K=1, x=24, y=-9, z=-

[VIII] *For the word classification task, data from 16 individuals was missing (6 reported No Abuse).*

15, Z = 5.36], hippocampal, (K=99, x=-21, y=-15, z=-18, Z >8), (K= 30, x=21, y=-12, z=-18, Z = 6.89), and mPFC activations (K= 738, x=-6, y=60, z=30, Z>8); (K= 57, x=-27, y=0, z=57, Z=7.67) & (K= 38, x=-39, y=36, z=30, Z=6.45). Table S2 depicts main effect of task activations outside our ROIs.

CEM AND WORD ENCODING: AMYGDALA AND HIPPOCAMPUS

Extracted amygdala and hippocampal activations for the main effect of task (SCR_pos>baseline, SCR_neg>baseline, and SCR_neu>baseline) were analyzed in a CEM (No abuse, CEM)×Words (Positive, Negative, Neutral)×Lateralization (Left, Right) RM ANCOVA, with psychiatric status (demeaned within group), age, and education level as covariates. Contrary to our expectations, there were no significant main, nor interaction effects of CEM [Amygdala (F's<1.26, all P's>.26) & Hippocampus (F's< 2.25, P's>.14), details in Supplement].

CEM AND WORD ENCODING: MPFC

A CEM vs. No Abuse analysis showed CEM related mPFC hypoactivation during the encoding of positive, negative and neutral words (K=15, x=-3 y=45 z=33, Z=3.82, Psvc=.034, Figure 1)[IX]. No other clusters were found in, or outside, our ROIs (Table 2).

A CEM (No Abuse, CEM)×Words (positive, negative, neutral) RM ANCOVA on extracted mPFC activations in this cluster, with psychiatric status (demeaned within group), age, gender, and education level as covariates showed, besides the main effect of CEM (F(1,188)=12.21, P=.001), a main effect of Words (F(2, 376) =4.54, P=.01). Positive words elicited more mPFC activation (M=.34, SE=.06) compared to neutral (M=.18, SE=.06; P<.005), but not negative words (M=.27, SE=.06, P=.42). No other differences were found (P's>.14). There was no Words×CEM interaction nor other significant main or interaction effects (F's< 2.25,P's>.11). Current psychiatric status had a main effect on mPFC activation (F(1,187)=7.13, P=.01); HC had more mPFC activations than patients (t's>3.05,P's<.003).

Additional covariance analyses showed that the main effect of CEM remained when we covaried for depression or anxiety severity, neuroticism scores, parental psychopathology, negative life events, concurrent physical and/or sexual abuse, antidepressant medication use, or mPFC volume in the CEM group (see Supplement).

Finally, to investigate the functional connectivity of this mPFC cluster (x=-3 y=45 z=33) in individuals with CEM (compared to No Abuse), we performed a Psycho–Physiological interaction (PPI) analysis (specifics in supplement; Friston et al., 1997)[X]. Across participants, the PPI showed

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[IX] *The mPFC activations for encoding and recognition were small volume corrected using a mask based on the Left Superior Frontal Medial cortex, 584 voxels, region based on AAL toolbox.*

[X] *Due to technical problems with fMRI data of 3 participants (1 reported CEM), we could not include these participants in the PPI analyses.*

positive connectivity with the right amygdala (K=9, x=21, y=0, z=-15, Z=3.87, Psvc<.004), and left hippocampus (K=17, x=-24, y=-12, z=-18, Z=3.97, Psvc<.02). No negative connectivity was found with our ROIs. However, no differential connectivity was found for the CEM versus No abuse groups within our ROIs (Supplement and Table S3).

Table 2. Whole brain effects of CEM vs No Abuse (F) at p<.005, K>5.

		K	F	Z	P	x,y,z
Encoding	Medial Frontal Gyrus	24	14.57	3.62	<.001	-3 45 33
	superior Temporal Gyrus	24	14.02	3.54	<.001	57 -51 9
	Inferior Frontal Gyrus	10	12.39	3.31	<.001	-51 30 0
	Insula	12	12.33	3.3	<.001	39 -27 6
			10.6	3.04	0.001	39 -27 18
	Middle Temporal Gyrus	5	10.15	2.96	0.002	-54 -9 -15
Recognition	Medial Frontal Gyrus	109	16.52	3.87	<.001	-6 48 39
			13.6	3.48	<.001	-6 30 45
			12.24	3.29	0.001	-3 39 45
	Superior Frontal Gyrus	6	9.72	2.89	0.002	-24 57 15
	Inferior Parietal Lobe	5	9.37	2.83	0.002	36 -45 45

RECOGNITION

MAIN EFFECT OF TASK DURING WORD RECOGNITION

The main effect of task during recognition was associated with mPFC activations (K=127, x=-3, y=27, z=48, Z=6.80); (K= 54, x=-30, y=-3, z=57, Z=6.70); (K= 43, x=3, y=63, z=3, Z=6.54); (K= 49, x=33, y=48, z=30, Z=6.43), but not with amygdala, nor hippocampal activations. Table S2 displays task activations outside our ROIs.

IMPACT OF CEM ON WORD RECOGNITION IN THE MPFC

A CEM vs. No Abuse analysis showed CEM related mPFC hypoactivation during the correct recognition of positive, negative and neutral words (K=48, x=-6 y=48 z=39, Z=4.03, P_{SVC}=0.0094, Figure 1). No other significant clusters were found in, or outside our ROIs (see Table 2).

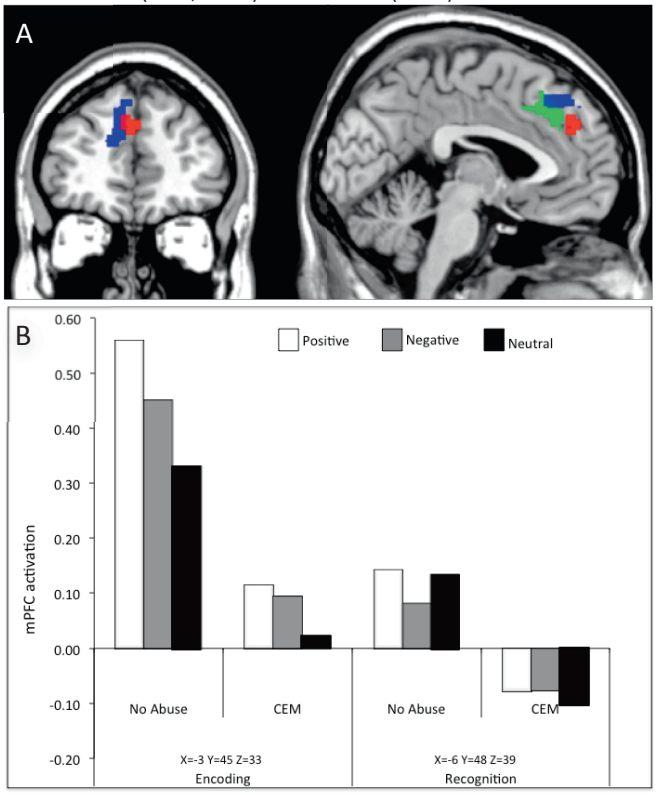
Next, we performed a CEM (CEM vs. No Abuse)×Words (Positive, Negative, Neutral) RM ANCOVA on extracted mPFC activations, with psychiatric status (demeaned within group), age, gender, and education level as covariates. Besides the main effect of CEM (F(1,188)=7.03, P=.01), there was no main effect of Words (F(2, 376) =.41, P=.69). Psychiatric status did have a main effect (F(1,188)=8.35, P=.004), with HCs having higher mPFC activations than patients (t's>2.79, P's<.006). Furthermore, gender had a main effect (F(1,188)=4.49, P=.04), with males having more mPFC activation than females (CE=-.18, P=.03). There was no Words×CEM interaction, nor other main, or interaction effects (Fs < 1.06, P's>.19).

Follow up covariance analyses showed that CEM related hypoactivation could not be explained by more depression or anxiety severity, neuroticism scores, parental psychopathology, negative life events, concurrent physical

and/or sexual abuse, antidepressant medication use, nor mPFC volume (Supplement).

Finally, a PPI analysis in this mPFC cluster (x=-6, y=48, z=39), revealed positive connectivity with the left amygdala (K=11, x=-27, y=0, z=-18, Z=3.64, Psvc<.009), and left hippocampus (K=22, x=-21, y=-12, z=-24, Z=4.98, Psvc<.005), but no negative connectivity with the mPFC, across participants. Finally, no CEM related differential connectivity was found within our ROIs (see Supplement and Table S4)

Figure 1. Medial prefrontal cortex activations during encoding, and recognition of positive, negative and neutral words in adults reporting Childhood Emotional Maltreatment (CEM; N=96) vs. No Abuse (N=98).



Note. Figure 1a depicts the main effect of CEM on medial prefrontal cortex activation during encoding (Red), and recognition (Blue) at P<.005 K>5 uncorrected. The green blob depicts the region that has been found to be smaller in adults reporting CEM (van Harmelen van Tol et al., 2010). Figure 1b depicts the medial prefrontal cortex activations (BOLD signal change) during encoding (Red), and recognition (Blue) of positive, negative, and neutral words in adults reporting CEM vs No Abuse.

DISCUSSION

We show consistent CEM related mPFC hypoactivation during the encoding and recognition positive, negative, and neutral words, a task that requires higher order cognitive processing. Our findings cannot be explained by CEM related higher levels of neuroticism, parental psychopathology, negative life events, concurrent physical and/or sexual abuse, antidepressant medication use, nor smaller mPFC volume (Van Harmelen, Van Tol, et al., 2010). In addition, the mPFC hypoactivations were not accounted for by psychiatric status, nor by higher depressive or anxiety symptoms, despite the fact that the CEM group contained more patients, and that patients showed mPFC hypoactivation compared to HC.

Contrary to our predictions limbic activations were not enhanced, and PPI analyses showed no CEM related differential mPFC-amygdala coupling either. Therefore, and together with findings of CEM-related amygdala hyperactivity to facial expressions (Bogdan et al., 2012; Dannlowski, Kugel, et al., in press; Dannlowski, Stuhrmann, et al., 2012; McCrory et al., 2011, 2013; Van Harmelen et al., 2012), these findings suggest that individuals reporting CEM show hypoactive mPFC activation during cognitive processing/evaluation for meaning/content (subserved by the mPFC), and hyperactive amygdala activation in response to emotionally demanding tasks or contexts, which require amygdala processing. Interestingly, this pattern of findings resembles those of studies on the impact of acute stress exposure, showing that stress exposure induces a shift from higher cognitive to more habitual/emotional processes, and related neural systems (PFC vs. limbic regions) (Hermans et al., 2011; Oei et al., 2012).

Individuals reporting CEM showed similar response accuracy and RTs for positive, negative and neutral words. Thus, although enhanced negative stimuli processing and related brain activations has been reported in depressed individuals (see for an overview: Groenewold, Opmeer, De Jonge, Aleman, & Costafreda, 2013), and in post-traumatic stress disorder (PTSD) (see for an overview: Brown & Morey, 2012), we did not find support for CEM related biased processing of negative stimuli. It is unclear whether this reflects a lack of biased processing, or whether the task at hand was not sensitive enough to detect biases. The classification task did not assess appraisal of the words; hence, even though participants know how to accurately categorize the words they may still appraise them as more negative. In addition, recognition was assessed after a short (ten minute) retention interval, making our task prone to performance ceiling effects that may obscure performance biases.

We found CEM related mPFC hypoactivation across valence, 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 processing in these individuals; individuals reporting CEM may require less cognitive and

related mPFC processing in order to correctly recognize words later on. It is unknown whether this overall blunting of mPFC activation translates to other cognitive domains, which one might expect given that the mPFC is also implicated in self-referential processing, and mentalizing (Denny, Kober, Wager, & Ochsner, 2012; Frith & Frith, 2006; Frith & Frith, 2003; Meyer et al., 2012; Mitchell, Macrae, & Banaji, 2006). Future studies are needed to investigate whether CEM related mPFC hypoactivation is related to dysfunctions in these forms of social cognitive processing, as this may have important clinical implications.

Some limitations need to be taken into account. First, retrospective self-reported CEM is innately subjective, and patients may over-report CEM histories. However, maltreatment history is more likely to be under than over-reported (Brewin, 2007; Hardt & Rutter, 2004), and in the NESDA (N=2981) CEM recall was not affected by current mood state (Spinhoven et al., 2010). Second, IQ was not assessed as a potential confound in our analyses. However, education level, which is highly correlated with IQ (r=.88; Gottfredson, 1997), did not explain our findings. Third, our cross-sectional design obscures causality inferences; mPFC hypoactivation may have been present before CEM, and may even be a predisposing factor that enhances parental risk to emotionally maltreat their children. However, continuing this line of reasoning, it might be expected that parental psychopathology is related to our findings, and it was not. Theoretically, only longitudinal studies can disentangle the impact of CEM from its predisposing factors. However, these studies are highly problematic from an ethical point of view, hence, our cross-sectional study with a large sample of patients and HCs, and control of many potential confounds is a good alternative.

Conclusion

We found that CEM is related to mPFC hypoactivation during the encoding and recognition of positive, negative and neutral words. This was not explained by higher depression or anxiety symptoms, neuroticism, parental psychopathology, negative life events, antidepressant use, nor by mPFC volume. Together with previous findings of CEM related smaller mPFC volume (Van Harmelen, Van Tol, et al., 2010), and amygdala hyperactivity to facial expressions (Bogdan et al., 2012; Dannlowski, Kugel, et al., in press; Dannlowski, Stuhrmann, et al., 2012; McCrory et al., 2011, 2013; Van Harmelen et al., 2012), these findings suggest that CEM increases individuals risk to the development of psychopathology (Iffland et al., 2012; Spinhoven et al., 2010) on differential levels of processing in the brain; mPFC hypoactivation during cognitive processing, or more basal amygdala hyperactivation during emotion processing. Therefore, our findings add substantively to the understanding of the long-term impact of CEM.

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Supplement

Additional exclusion criteria

Clinical criteria

Patients were excluded from the NESDA-MRI sample if they had an axis-I disorder other than MDD, panic disorder or social phobia (except generalized anxiety disorder). Patients were also excluded if they used any psychotropic medication other than a stable use of SSRI or infrequent benzodiazepine use (3×2 tablets weekly, or within 48 hrs prior to scanning). Additional exclusion criteria were the presence of major internal or neurological disorders; dependency or past year abuse of alcohol and/or drugs; hypertension (>180/130mm Hg); heavy smoking (>5 cigarettes/day); and general MRI-contra-indications.

Technical criteria

We had complete word encoding and recognition data (EPIs and e-prime output) for 286 participants (data of 15 participants was incomplete). In addition, 61 participants were excluded because of 1) bad quality of the EPI data acquired during encoding and/or recognition (n=22), 2) movement >3mm (n=6), 3) not enough coverage of the hippocampus and amygdala (n=4), 4) loss of voxels in the first level mask, owing to large inter-hemispheric frontal space (n=1), 5) very low discriminant power (i.e. d'=<.1; n=17) or >40 missing responses (n=7) indicating unreliable task involvement, 6) medication use (n=2; 1× mirtazepine, 1× corticosteroids), 7) MADRS scores of HC (n=2) that were indicative of possible depressive psychopathology, leaving data of 225 participants suitable for the present analysis. Of these 225, 98 participants reported to have never experienced abuse in their lives, and 111 participants reported to have experienced chronic childhood abuse. Because we were primarily interested in the impact of CEM, we excluded individuals reporting physical and/or sexual abuse during childhood, but no CEM (n=15).

Word encoding and recognition task

All words were matched for length (3-12 letters), and frequency of occurrence in the Dutch language. The words were presented pseudo-randomized together with 40 baseline trials in 20 blocks of eight words, and with an average interstimulus interval of 1026 ms (1018 ms-1035 ms). During each block, two positive, two negative, two neutral, and two baseline words were presented, with response options presented at the bottom of the screen. Participants were required to indicate whether they thought the word was positive, negative, or neutral. To protect against primacy and recency effects, we presented three filler words (1 positive, 1 negative, and 1 neutral word) at the beginning and end of the encoding task. These filler words were not part of the recognition task.

After a ten minutes retention interval, participants completed a word recognition task. This task consisted of the 120 old encoding target words

and 120 new distracter words, and 40 baselines, presented in a pseudo-randomized order of 20 blocks of 14 words. Old and new words were matched on their complexity, word length, and emotional intensity. Subjects had to indicate whether they have 'seen' (i.e. remembered) the words previously, 'probably have seen it' ('know'), or 'haven't seen it' (rejection). No feedback was presented to the participants. Participants' responses and reaction times (RT) were registered through two magnet-compatible response boxes.

Before and after the word encoding-recognition task, we also monitored anxiety levels using a Visual Analogue Scale (VAS; Huskisson, 1993) ranging from zero to 100. Task instructions were presented inside the scanner and participants had the opportunity to ask questions before the task started. The encoding-recognition paradigm was part of a larger functional and structural imaging, results of that are reported elsewhere. The word task was presented after a neutral executive functioning task, (i.e. the tower of London task). In addition, the effect of psychiatric status on word encoding and recognition are described by van (Van Tol et al., 2012).

MEMORY PERFORMANCE AND REACTION TIMES ANALYSES

A CEM (CEM vs. No Abuse)×Words (Positive, Negative, Neutral) RM ANOVA, with a dummy demeaned for variability due to current diagnosis within group, age, gender and education as covariates showed a marginal effect of CEM on old/new discriminant sensitivity ($F(1, 188)=3.01$, $P=.08$). Overall, individuals reporting CEM were slightly more accurate to detect old words from new words (Mean= .61, SE= .013) when compared to individuals reporting No Abuse (Mean= .58, SE= .013).

There was no main effect of Words ($F(2, 376)=.68$, $P=.51$), nor a interaction between CEM and Words ($F(2, 376)=.48$, $P=.62$). When we repeated this analysis for proportions (p) Correctly Recognized words (pCREC), CEM and Words had no significant main effects [i.e. CEM ($F(1, 188)=1.12$, $P=.29$), Words ($F(3,276)=.73$, $P=.48$)], and there was no CEM×Words interaction ($F(2, 376)=1.11$, $P=.33$). When we repeated the analysis for proportion of false alarms, only a main effect of Words was obtained ($F(2, 376)=3.53$, $P=.03$). All individuals had fewer false alarms with positive words (M=.73, se=.01), when compared to negative (M=.69, SE =.01, P=.00), and neutral words (M=.70, SE =0.1, P=.00). CEM did not have a significant main effect ($F[1, 188]=1.21$, $P=.27$). There was no CEM×Words interaction ($F(2, 376)=1.32$, $P=.27$).

When we repeated the analysis for RT for subsequently correctly recognized words during encoding, no main effect was found for CEM ($F(1, 188)=.01$, $P=.92$). A main effect was found for Words ($F(2, 376)=6.57$, $P=.002$). All individuals responded quicker to negative words (M=1.26, SE=.02) when compared to positive (M=1.32, SE=.02, P=.00), and neutral words (M=1.33, SE=0.2, P=.00). There was no CEM×Words interaction ($F(2, 376)=.68$, $P=.51$). Finally, we found no significant main nor interaction

effects of CEM or Words when we repeated the analysis for RT of false alarms (all F's <.84, all P's>.42).

CEM AND WORD ENCODING: AMYGDALA AND HIPPOCAMPUS, ADDITIONAL FINDINGS.

The CEM (No abuse, CEM)×Words (Positive, Negative, Neutral)×Lateralization (Left, Right) RM ANCOVA with a dummy for diagnosis, age, and education level as covariates for both bilateral (i.e. left and right) amygdala and bilateral hippocampal activations showed no main effect of lateralization [i.e. Amygdala: (F(1, 189)=0.18, P=.89), Hippocampus: (F(1, 189)=0.13, P=.91)]. Psychiatric status did have a main effect on amygdala and hippocampal activation [Amygdala: (F(1, 189)=7.71, P=.006) & Hippocampus: (F(1, 189)=6.47, P=.01)]. Patients showed less bilateral amygdala and hippocampal activation during the encoding of positive words (t's>2.5, P's<.013), but not during encoding of negative words (t's<1.22, P's>.22; consistent with 28). During the encoding of neutral words, patients showed reduced bilateral amygdala activation (t's>2.08, P's<.04), marginal reduced right hippocampal activation (t=1.7, P=.08), but not differential left hippocampal activation (t=1.6, P=.11).

Table S1. Reaction times for the encoding and recognition tasks.

encoding	M	SD	M	SD	F	P
Subsequent remembered positive words	1.47	0.35	1.45	0.35	0.09	0.77
Subsequent remembered negative words	1.26	0.29	1.31	0.40	0.87	0.35
Subsequent remembered neutral words	1.52	0.32	1.59	0.42	1.86	0.17
Baseline trials in encoding phase	0.84	0.21	0.85	0.38	0.12	0.73
recognition						
Correctly recognized positive words	1.32	0.24	1.33	0.27	0.02	0.88
Correctly recognized negative words	1.25	0.22	1.27	0.30	0.41	0.52
Correctly recognized neutral words	1.32	0.23	1.34	0.30	0.15	0.70
Misses positive recognition words	1.92	0.59	1.89	0.64	0.14	0.71
Misses negative recognition words	1.86	0.66	1.82	0.56	0.18	0.68
Misses neutral recognition words	1.72	0.53	1.63	0.60	1.19	0.28
False alarms positive words	1.50	0.46	1.65	0.57	4.03	0.05
False alarms negative words	1.51	0.49	1.47	0.42	0.40	0.53
False alarms neutral words	1.57	0.51	1.56	0.47	0.01	0.92
Baseline trials in recognition phase	0.79	0.14	0.81	0.37	0.30	0.59

ADDITIONAL COVARIANCE ANALYSES FOR WORD ENCODING AND RECOGNITION

For all additional covariance analyses (see below) we repeated the CEM (No Abuse vs. CEM)×Words (positive, negative, neutral) RM ANCOVA on mPFC activations, with a demeaned dummy for diagnosis, age, gender, education level, and the additional variable as covariates. Because of the large amount of covariates that we wanted to investigate, we choose to perform separate analyses per covariate because we believe this is a more stringent way to investigate the possible impact of each covariate.

DEPRESSION AND ANXIETY SEVERITY

To exclude the possibility that more severe depressive symptoms in the CEM groups explained our findings, we added depression severity (MADRS instead of psychiatric status) at the moment of scanning as a covariate to the RM ANCOVA. In this analysis all results remained, including the main effect of CEM for encoding ($F(1,189)=7.72$, $P=.006$, $d=.40$) and recognition ($F(1,189)=6.43$, $P=.012$, $d=.37$). Moreover, depression severity at the moment of scanning did not have a main effect on mPFC activation during encoding ($F(1,189)=1.65$, $P=.20$) and recognition ($F(1,189)=.06$, $P=.80$).

Similarly, all results remained when we added anxiety severity at the moment of scanning to the analysis (i.e. main effect of CEM during encoding ($F(1,181)=10.28$, $P=.002$, $d=.46$) and recognition ($F(1,181)=7.69$, $P=.006$, $d=.40$). Anxiety severity at the moment of scanning had a marginal effect on mPFC activation during encoding ($F(1,181)=3.24$, $P=.07$), but not during recognition ($F(1,181)=.69$, $P=.41$).

NEUROTICISM

To investigate whether our results were driven by higher neuroticism scores in the CEM group, we next repeated the RM analyses while covarying for neuroticism score. In these analyses, all results remained, including the main effect of CEM for word encoding ($F(1, 187)=16.73$, $P<.001$ $d=.59$), and word recognition, albeit now a small effect ($F(1, 187)=3.98$, $P=.047$, $d=.03$). In addition, Neuroticism was a significant covariate for emotional word encoding ($F(1, 187)=4.31$, $P=.04$), but not for word recognition ($F(1, 187)=.24$, $P=.62$).

PARENTAL PSYCHOPATHOLOGY

To investigate whether parental psychopathology was related to our findings, we added parental psychopathology (yes, no) as a covariate to the RM ANCOVAs. In these analyses, hypoactive mPFC activation in adults reporting CEM remained for word encoding ($F(1,128)=6.46$, $P=.012$) and recognition ($F(1,128)=8.39$, $P=.004$). Furthermore, parental psychopathology had no significant main effect during encoding ($F(1,128)=.04$, $P=.84$), and recognition ($F(1,128)=.67$, $P=.41$).

SMALLER MPFC VOLUME IN THE CEM GROUP

To investigate whether CEM related reduced mPFC activation during emotional word encoding would be explained by a volumetrically smaller mPFC in these individuals (Figure 1), we added mPFC volume as a covariate to the RM ANCOVAs. In these analyses all results remained unchanged, including the main effect of CEM during word encoding ($F(1,187)=13.43$, $P<.001$, $d=.53$) and word recognition ($F(1,187)=6.68$, $P=.01$, Cohen's $d(d)=.37$), Furthermore, structural volume of the mPFC had no significant main effect on mPFC activation during word encoding ($F(1,187)=2.63$, $P=.11$), nor word recognition ($F(1,187)=.23$, $P=.63$).

Concurrent other types of abuse

To examine whether our results were driven by concurrent physical and/or sexual abuse, we next excluded individuals reporting sexual and/or physical abuse besides CEM (n=40) from RM ANCOVAs. In these analyses, all results remained unchanged, including the effect of CEM on mPFC activation during word encoding ($F(1,148)=7.73$, $P=.01$, $d=.47$), and recognition ($F(1,147)=6.32$, $P=.01$, $d=.42$).

More negative life events

To investigate if more negative lifetime life events in the CEM group explained our findings we next repeated the RM ANCOVAs while adding the total number of lifetime life events as covariate. The analyses did not change our results including the main effect of CEM during encoding ($F(1,186)=11.94$, $P=.001$, $d=.05$), and recognition ($F(1,186)=6.72$, $P=.01$, $d=.37$). Number of lifetime negative life events did not have a significant main effect on mPFC activation during encoding ($F(1,186)=.37$, $P=.55$), nor recognition ($F(1,186)=1.08$, $P=.30$).

SSRI use

To explore the impact of SSRI use on our findings, we repeated all RM ANCOVAs while excluding SSRI users from the analysis (n=50). In these analyses all results remained, including the main effect of CEM for word encoding ($F(1,138)=5.76$, $P=.02$, $d=.50$), and word recognition ($F(1,138)=5.98$, $P=.02$, $d=.44$) in mPFC hypoactivation.

Psycho-Physiological Interaction analyses

We used psycho-physiological interaction analyses to investigate the functional connectivity of the CEM related mPFC clusters that we found to be hypoactive during encoding, and retrieval, and to investigate whether these mPFC clusters showed differential functional connectivity for adults reporting CEM vs. No Abuse. For these PPI analyses, we used the deconvolved time series from a 8 mm radius sphere around the CEM related mPFC cluster (i.e. encoding (x=-3, y=45, z=33), recognition (x=-6, y=48, z=39)). The PPI was calculated as the product of the mPFC time series (the first eigenvariate from all voxels' time series) and a vector coding for the effect of task ("Subsequently remembered emotional words>baseline"). Because of the fact that we found no effect of valence in mPFC activation during encoding, nor retrieval, we investigated mPFC connectivity patterns irrespective of valence (positive, negative and neutral together). This product of the mPFC time series was subsequently re-convolved with the hemo- dynamic response function (HRF). This interaction term was then entered as a regressor in a first level model together with the time series of the mPFC and the vector coding for the task effect. The models were estimated and contrasts generated to estimate the effects of positive and negative PPIs. These subject specific maps represent stronger positive and

negative functional connectivity with the mPFC for an emotional compared to a baseline words. The contrast images for the PPI effects were then entered in a second level two-group t-test analysis. Subsequently, positive and negative brain connectivity with the mPFC was tested at P=.001, with a spatial extend of K>5 contiguous voxels for ROIs (i.e. Hippocampus and Amygdala, masks defined using the WFU pickatlas). Furthermore we report activation outside our ROIs at $P< 0.05$, $K \geq 5$ voxels corrected for multiple comparisons.

Table S2. Main effects of encoding and recognition outside our ROIs.

Encoding	K	Z	P	x,y,z
Middle Temporal Gyrus	6164	>8	<.001	60 -54 6
		>8	<.001	57 -57 -6
		>8	<.001	60 -48 15
Anterior Frontal Gyrus	386	>8	<.001	-51 24 0
		>8	<.001	-51 27 12
		7.46	<.001	-48 9 -27
Cuneus	1956	>8	<.001	-15 -96 6
		>8	<.001	-30 -90 -6
		>8	<.001	18 -93 9
Anterior Frontal Gyrus	967	>8	<.001	51 12 24
		>8	<.001	45 6 51
		>8	<.001	48 42 12
Middle Temporal Gyrus	16	6.71	<.001	-60 -9 -15
Insula	69	6.03	<.001	-45 0 0
		5.13	<.001	-36 0 12
		5.12	<.001	-42 -9 -12
Middle Temporal Gyrus	6	5.1	<.001	-45 -66 27
Insula	3	4.8	<.001	-33 -36 21
Caudate	1	4.7	<.001	15 18 15
Recognition	K	Z	P	x,y,z
Precuneus	3550	>8	<.001	3 -54 45
		>8	<.001	60 -57 0
		>8	<.001	60 -54 12
Inferior Parietal Lobe	895	>8	<.001	-48 -39 51
		>8	<.001	-57 -60 -3
		>8	<.001	-60 -54 12
Middle Occipital Gyrus	206	>8	<.001	-24 -93 0
		7.82	<.001	-12 -90 -3
		7.77	<.001	-15 -96 6
Cuneus	68	7.42	<.001	18 -96 3
		5.24	<.001	30 -90 -3
Inferior Frontal Gyurs	152	7.11	<.001	-45 45 3
		6.36	<.001	-36 21 -3
		6.08	<.001	-48 33 -3
Paracentral Lobule	127	6.8	<.001	-3 27 48
Superior Occipital Gyrus	11	5.76	<.001	-39 -81 24
Midde Temporal Gyrus		5.33	<.001	-45 -78 18
Cerebellum	37	5.73	<.001	24 -54 -18
Inferior frontal Gyrus	2	4.71	<.001	-51 27 21
Superior Temporal Gyrus	2	4.64	<.001	57 6 3
Superior Frontal Gyrus	1	4.59	<.001	-30 45 33

Table S3. Connectivity with the main effect of mPFC during encoding as seed region at P<.001, K>5.

	K	F	Z	P	x,y,z
Inferior Frontal Gyrus	130	33.22	5.40	<.001	45 33 -9
		20.00	4.20	<.001	54 18 0
		19.03	4.09	<.001	54 12 -6
Middle Frontal Gyrus	524	29.00	5.05	<.001	-42 12 36
		23.70	4.57	<.001	-27 21 -6
		22.65	4.47	<.001	-27 -30 -15
Medial Frontal Gyrus	434	26.10	4.80	<.001	-3 48 30
		24.92	4.69	<.001	-6 63 9
		23.03	4.51	<.001	0 21 51
Inferior Parietal Lobe	135	22.95	4.50	<.001	-51 -33 45
		18.04	3.98	<.001	-39 -39 39
		15.25	3.65	<.001	-39 -51 45
Superior Temporal Gyrus	19	22.90	4.50	<.001	42 15 -27
		13.31	3.40	<.001	36 3 -24
Superior Temporal Gyrus	217	21.23	4.33	<.001	-57 -60 24
		21.10	4.31	<.001	-57 -51 27
		18.39	4.02	<.001	-51 -54 21
Putamen	30	21.12	4.32	<.001	21 3 -12
Caudate	105	20.96	4.30	<.001	12 3 3
		18.44	4.03	<.001	12 18 6
		13.77	3.46	<.001	18 0 12
Putamen	61	19.15	4.11	<.001	-15 12 0
		15.37	3.66	<.001	-15 -3 15
Superior Temporal Gyrus	22	18.65	4.05	<.001	45 -21 -3
Inferior Temperal Gyrus	53	18.36	4.02	<.001	-48 -66 -6
		14.49	3.55	<.001	-45 -75 -6
		13.39	3.41	<.001	-48 -57 3
Superior Temporal Gyrus	9	17.16	3.88	<.001	42 3 -15
Medial Frontal Gyrus	22	17.03	3.86	<.001	-3 54 -6
	23	16.87	3.85	<.001	30 -45 -9
Inferior Frontal Gyrus	14	16.63	3.82	<.001	57 18 18
Fusiform Gyrus	10	16.46	3.80	<.001	-24 -66 -15
Middle Temporal Gyrus	29	16.27	3.77	<.001	-51 3 -21
		16.03	3.74	<.001	-60 -6 -15
Superior Frontal Gyrus	10	14.85	3.60	<.001	-27 39 36
Middle Frontal Gyrus	13	14.79	3.59	<.001	-27 -6 48
Inferior Frontal Gyrus	7	14.40	3.54	<.001	30 21 -15
Middle Frontal Gyrus	13	14.39	3.54	<.001	-27 51 12
Thalamus	5	13.52	3.42	<.001	6 -21 6
Middle Temporal Gyrus	7	13.12	3.37	<.001	-54 -27 -6
CEM>No Abuse					
Thalamus		3.9	3.81	<.001	12 -3 3
Insula		3.84	3.76	<.001	42 -33 21
No Abuse > CEM no sigificant clusters					

Table S4. Connectivity with the main effect mPFC during recognition as seed region at P<.001, K>5.

	K	F	Z	P	x,y,z
Superior Frontal Gyrus	6880	53.25	6.73	<.001	0 30 51
		41.93	6.03	<.001	-3 9 51
		39.25	5.84	<.001	12 -15 9
Inferior Parietal Lobe	152	21.38	4.34	<.001	51 -39 45
		19.64	4.16	<.001	54 -48 42
		15.98	3.74	<.001	51 -24 48
Middle Occipital Gyrus	14	16.52	3.80	<.001	33 -84 -3
Middle Occipital Gyrus	10	15.55	3.69	<.001	-48 -72 3
Parahippocampal Gyrus	9	15.50	3.68	<.001	21 -15 -21
Precentral Gyrus	12	15.41	3.67	<.001	-18 -30 57
		13.22	3.38	<.001	-12 -39 57
Lingual Gyrus	10	15.21	3.64	<.001	12 -90 0
Precuneus	8	13.95	3.48	<.001	33 -72 33
Superior Frontal Gyrus	8	13.77	3.46	<.001	0 60 30
Fusiform Gyrus	19	13.71	3.45	<.001	-39 -69 -12
		12.01	3.21	<.001	-27 -66 -15
Insula	5	13.26	3.39	<.001	-36 -12 12
Putamen	5	12.65	3.30	<.001	27 -6 3
CEM > No abuse	No significant clusters				
No Abuse > CEM	No significant clusters				

Chapter 7: Enhanced mPFC reactivity to social rejection in young adult patients and controls reporting childhood emotional maltreatment

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Under Review

ABSTRACT

Children who have experienced chronic parental rejection and exclusion during childhood, as is the case in childhood emotional maltreatment (CEM), may become especially sensitive to social exclusion. This study investigated the neural and emotional responses to social exclusion in individuals reporting CEM using the Cyberball task. Using functional magnetic resonance imaging (fMRI), we investigated brain responses and self-reported distress to social exclusion in 46 young adults (mean age=19.2, SD=2.16) reporting low to extreme CEM. Consistent with prior studies, social exclusion was associated with activity in the ventral medial prefrontal cortex (mPFC) and posterior cingulate cortex. In addition, severity of a history of CEM was positively associated with increased dorsal mPFC responsivity to social exclusion. The dorsal mPFC plays a crucial role in self- and other-referential processing, suggesting that the more individuals have been rejected and maltreated in childhood, the more self- and other-processing is elicited by social exclusion in adulthood. Negative self-referential thinking, in itself, enhances cognitive vulnerability for the development of psychiatric disorders. Therefore, our findings may underlie the emotional and behavioural difficulties that have been reported in adults reporting CEM.

INTRODUCTION

Chronic parental rejection (active and/or passive) can be considered a core aspect of Childhood Emotional Maltreatment (CEM; emotional abuse and/or emotional neglect) (APSAC, 1995). For instance, during episodes of CEM, children may be ignored, isolated, or siblings may be favored. CEM has severe and persistent adverse effects on behavior and emotion in adulthood (Hart & Rubia, 2012), and CEM is a potent predictor of depressive and anxiety disorders in later life (Iffland, Sansen, Catani, & Neuner, 2012; Spinhoven et al., 2010). Social rejection, ranging from active isolation to passively ignoring a person, may enhance sensitivity towards future rejection (DeWall & Bushman, 2011). 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 (DeWall & Bushman, 2011). Furthermore, rejection sensitivity (both behaviourally and in terms of brain responses) is positively related to the development and maintenance of depression, social anxiety, and borderline personality disorder symptoms (Masten et al., 2011; 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 subjective and neural responses to social rejection in individuals reporting CEM are currently unknown.

Social rejection in the lab has been examined most frequently with the Cyberball task (Williams, Cheung, & Choi, 2000; Williams & Jarvis, 2006). During an fMRI compatible variation of the Cyberball task, participants play two games of virtual toss with two other players (computer controlled confederates). In the first (inclusion) game, participants are thrown the ball an equal number of throws as compared to the other players. However, in the second (rejection/exclusion) game they may receive the ball once or twice in the beginning of the game, but thereafter never receive it again. Social exclusion during the Cyberball task induces a cascade of negative emotions, including anxiety, depression, reduced sense of belonging and meaningful existence, and a reduced sense of control, and lowered self-esteem (Boyes & French, 2009; DeWall & Bushman, 2011; Moor et al., 2012; Themanson, Khatcherian, Ball, & Rosen, In Press; Zadro, Williams, & Richardson, 2004).

Neuroimaging studies have revealed a set of brain regions that are typically activated during social exclusion in the Cyberball task, primarily in cortical midline structures; the anterior cingulate cortex (ACC)/ medial prefrontal cortex (mPFC), and Insula (Cacioppo et al., 2013; Eisenberger, 2012). The ACC and mPFC are vital for expectancy-violation, error-detection, the processing of cognitive conflict, and self- and other referential processing (Etkin, Egner, & Kalisch, 2011; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Somerville, Heatherton, & Kelley, 2006). In line, a recent

meta-analysis suggested that activation in these regions during social exclusion might be related to enhanced social uncertainty, social distress, and social rumination (Cacioppo et al., 2013). Activation in the dorsal ACC/mPFC and Insula have been related to self-reported distress during exclusion in the Cyberball game, however, not all studies found dorsal ACC/mPFC responsivity to social exclusion (Cacioppo et al., 2013; Eisenberger, 2012; Masten, Eisenberger, Pfeifer, & Dapretto, 2010; Yoshimura et al., 2009), or only found it in the first trials of the exclusion game (Moor et al., 2012). Furthermore, studies investigating adolescents and children found ventral ACC/mPFC responses to distress during social exclusion (Bolling et al., 2011; Masten et al., 2009; Moor et al., 2012; Sebastian et al., 2011). Increased dorsal ACC/ mPFC to exclusion may be dependent on individual differences. As dorsal mPFC activity is especially pronounced in individuals sensitive to interpersonal rejection (Burklund, Eisenberger, & Lieberman, 2007; Eisenberger, Way, Taylor, Welch, & Lieberman, 2007), anxiously attached (DeWall et al., 2012), and/or having low self-esteem (Onoda et al., 2010; Somerville, Kelley, & Heatherton, 2010). Therefore, dorsal ACC/mPFC responsivity to social rejection may also be evident in individuals with CEM. However, CEM related brain functioning during social exclusion has not yet been examined.

We examined the impact of a history of CEM on brain functioning and emotional distress to social exclusion. We compared young adult patients reporting a moderate to extreme history of CEM (N=26) with healthy controls (N=20) reporting low to moderate CEM. We examined whole brain responses while specifying the mPFC, ACC and Insula as regions of interest (ROIs) because of their important role in social exclusion (Cacioppo et al., 2013; Eisenberger, 2012). We hypothesized that individuals reporting a history of CEM would show enhanced brain responses and emotional distress to social exclusion. Therefore, we hypothesized that the severity of CEM would show a dose-response relationship with self-reported distress and brain responsivity.

METHODS

SAMPLE

We included a total of 26 out- and inpatients reporting moderate to extreme CEM ('CEM group') who were in treatment at a center for youth specialized mental health care in the Hague, the Netherlands (mean age=18.31 years, SD=1.23; 6 males) and 20 healthy controls reporting low to moderate CEM (mean age=18.85, SD=1.95; 6 males). The CEM and control groups were matched in terms of age ($F(1,44)=1.38$, $P=.25$), gender ($X^2(1)=.28$, $P=.74$), and IQ ($F(1,44)=2.76$, $P=.10$) (see Table 1). In the CEM group, 11 patients reported regular use of anti-depressant and anti-anxiogenic medication (n=8 used SSRI's, n=1 used the tricyclic antidepressant (TCA) = amitrypteline, and n=3 used benzodiazepam).

Table 1. Demographics for the Control and CEM groups.

	Controls (n=20)		CEM (n=26)				
	Mean	SD	Mean	SD	X^2	F	P
Gender M/F	6/14		6/20		.281		0.74
IQ	111.5	9.54	107.0	8.76		2.76	0.10
Age	18.85	1.90	18.31	1.23		1.38	0.25
Emotional Abuse	5.2	0.89	11.81	4.20		47.70	0.00
Emotional Neglect	6.85	1.76	17.65	3.60		151.81	0.00
Physical Abuse	5.00	0.00	6.38	2.65		5.41	0.03
Physical Neglect	4.05	0.22	6.77	3.90		9.64	0.00
Sexual Abuse	5.45	1.00	9.15	2.66		34.75	0.00

Patients in the CEM group were excluded when they had a comorbid pervasive developmental disorder or psychosis (as measured with the SCID-I; Spitzer, Williams, Gibbon, & First, 1990). In addition, current substance abuse was also set as an exclusion criterion. Current substance abuse was measured through random urine samples that are mandatory for individuals admitted at the center.

Fifteen participants from the control group had participated earlier in a study on developmental differences in neural responses during social exclusion (Gunther Moor et al., 2012). Twenty-six participants who were >15 years of age at the time of scanning in the Gunther Moor et al. study, and who had indicated that they could be approached for future research were contacted. Twenty-one participants agreed to participate and completed the Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998). Five participants were excluded based on CTQ scores indicating a history of childhood abuse; two reported moderate to severe physical abuse (both scored 12), two reported severe emotional neglect (both scored 19), and one reported borderline moderate/severe emotional neglect (14). To further obtain a good match with the CEM group, five control participants were recruited from the general public through a recruitment website, and through adevertisements. All control participants included in this study indicated no history of psychiatric disorder, were not taking any psychotropic drugs and had scores of low-moderate emotional abuse (<12), emotional neglect (<14), and physical neglect (<10), and no physical abuse (<6), and sexual abuse (<6), on the CTC according to the American cut offs (Bernstein & Fink, 1998).

Finally, exclusion criteria for all participants were left-handedness, or general contra-indications for MRI, such as metal implants, heart arrhythmia, and claustrophobia, difficulty understanding the Dutch language, or a IQ < 80 (all participants completed the WAIS, or if <18 years the WISC intelligence subscales similarities and block design; Wechsler, 1991, 1997). All participants provided written informed consent, and the Leiden University Medical Center Medical Ethics committee approved this study.

ASSESSMENT OF PSYCHOPATHOLOGY

In all patients with a history of CEM, DSM-IV axis 1 (psychiatric disorders) and DSM-IV axis II disorders (personality disorders) were assesed using the Structured Clinical Interview for DSM Disorders (SCID-I & SCID-II; First & Gibbon, 1997; Spitzer et al., 1990). All patients in the CEM group had at least one axis I disorder (18 participants had multiple axis I disorders), and 19 participants had a concurrent axis II personality disorder (see Table 2 for all axis I and II diagnoses). Control participants over the age of 18 at the time of scanning reported no history of neurological or psychiatric disorders.

Table 2. Clinical characteristcs of the CEM group.

SCID I	Depression	Alcohol abuse	Social phobia	Obsession	Generalized Anxiety	PTSD	
# current	16		10	2	1	10	
# Lifetime	9	3	4	1		3	
Total	24	3	14	3	1	13	
SCID II	Avoidant	Dependent	Obsessive	Depressive	Passive Agressive	Paranoid	Borderline
	11	2	3	10	1	5	7

Note. Scid II data for 2 participants was missing

Control participants who were under the age of 18 at the time of scanning were screened for psychiatric disorders using the Child Behavioural Checklist (CBCL; Achenbach, 1991) that was filled in by their parents. Control participants were only included in this study if they scored in the normal range of the CBCL. Control participants over the age of 18 at the time of scanning were screened for DSM-IV axis II personality disorders with the Dutch Questionnaire for Personality Characteristics (Vragenlijst voor Kenmerken van de Persoonlijkheid (VKP); Duijsens, Eurelings-Bontekoe, & Diekstra, 1996). Because the VKP is known to be overly inclusive (Duijsens, Eurelings-Bontekoe, & Diekstra, 1996), controls with a score that indicated a 'probable' personality disorder on the VKP (n=8) were also assessed with a SCID-II interview by a trained clinical psychologist (K.H.). All controls that were followed up with the SCID-II were free from personality disorder diagnoses.

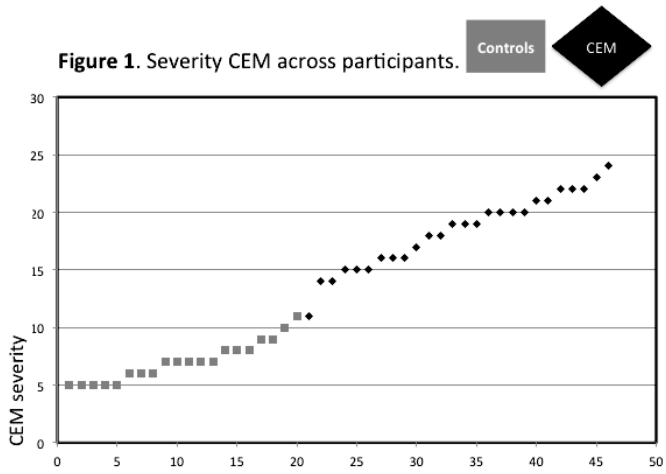
CHILDHOOD EMOTIONAL MALTREATMENT

History of childhood emotional maltreatment was assessed using the Dutch version of the Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998). In the Dutch version of CTQ (Arntz & Wessel, 1996), a total of 24 items are scored on a 5-point scale, ranging from 1=never true to 5=very often true. The CTQ retrospectively assessed five subtypes of childhood abuse: emotional abuse, sexual abuse, physical abuse, emotional neglect and physical neglect. The CTQ is a sensitive and reliable screening questionnaire with Cronbach's alpha for the CTQ subscales varying between .63-.91 (Thombs, Bernstein, Lobbestael, & Arntz, 2009).

In line with the American Professional Society on the Abuse of Children (APSAC, 1995) and our previous studies on CEM (Van Harmelen, Elzinga,

Kievit, & Spinhoven, 2011; Van Harmelen et al., 2010), emotional maltreatment in childhood was defined as a history of emotional neglect and/or emotional abuse before the age of 16 years. For the entire sample, overall CEM score (i.e. severity) was defined as the highest score on the emotional abuse or emotional neglect subscale of the CTQ (e.g., if emotional abuse score was 19, and emotional neglect score was 14, overall CEM score was 19). In our study, Cronbach's alpha for the emotional abuse subscale was .88, for the emotional neglect subscale .94, and for the combined emotional abuse and neglect subscales .83. The CEM group reported significantly higher levels of childhood abuse compared to controls on all subscales of the CTQ (all F's>5.41, P's<.03) see Table 1. Self-reported CEM ranged from low to extreme CEM across participants (see Figure 1). In the control group self-reported severity of CEM ranged from low to moderate, whereas in the CEM group severity of CEM ranged from moderate to extreme (Bernstein & Fink, 1998).

Figure 1. Severity CEM across participants.



THE CYBERBALL GAME

In the Cyberball game (Williams et al., 2000; Williams & Jarvis, 2006) participants played a game of virtual toss with two other players (computer controlled confederates), depicted using animated avatars. Participants were led to believe that the other players (one female, one male) played the game online on the Internet. Fictitious names of the players (common Dutch names, counterbalanced between participants) were displayed on the screen just above their avatars (i.e. in the left and right hand corners of the screen). The participant's self was displayed on the screen as an animated hand, with the participant's name displayed just below the hand. In the Cyberball game, participants first played the inclusion game, followed by the exclusion game. During inclusion, participants threw the ball one-third of the total amount of throws (thus, achieving an equal number of throws as compared to the other players). During social exclusion, they received the ball once in the

beginning of the game, but thereafter never received it again. Immediately after inclusion, and after exclusion, participants filled in two questionnaires that assessed their distress during the game (see below for specifics on the questionnaires). All instructions, and questionnaires were presented on the screen, and all instructions were read out loud (through the intercom) by the experimenter. Finally, and before starting the Cyberball game, participants were questioned whether they understood the instructions of the game.

Both Cyberball games consisted of a total of 30 ball tosses, and each game was administered in a separate run that lasted circa 5 minutes. The duration of each ball toss was fixed to 2 seconds. We added a random jitter interval (100-4000 ms.) in order to account for the reaction time of a real player. To further increase credibility of the Cyberball game, both games started with a loading screen that notified that 'the computer is trying to connect with the other players'.

DISTRESS: NEED SATISFACTION AND MOOD RATINGS

To assess distress after inclusion, exclusion, and after scanning (just before the debriefing; 'post scanning'), all participants completed the Need Threat Scale (Van Beest & Williams, 2006), and a mood questionnaire (Sebastian, Viding, Williams, & Blakemore, 2010). The need threat questionnaire consists of eight items that measure self-esteem, belonging, meaningful existence, and control (each was measured with two questions). The mood questionnaire consisted of eight items that (two of each) measured feeling good/bad, relaxed/tense, happy/sad, and friendly/unfriendly. All items on the questionnaires were rated from 1 ('not at all') to 5 ('very much'), and a high score on both questionnaires indicates good mood, or high needs threat[XI].

After inclusion and exclusion, participants were instructed to describe their mood and need threat feelings during the inclusion and exclusion game. At post-scanning, participants were instructed to assess their current mood and need threat feelings.

FMRI DATA ACQUISITION

Upon arrival to the lab, we first familiarized the participants with the scanning environment and sounds, using a mock scanner, and recorded scanner sounds. Actual scanning was performed on a 3.0 Tesla Philips fMRI scanner in the Leiden University Medical Center. To restrict head motion, we inserted foam cushions between the coil and the head. Functional data were acquired using T2*-weighted Echo-Planar Images (EPI) (TR = 2.2 s, TE = 30 ms, slice-matrix = 80 × 80, slice- thickness = 2.75 mm, slice gaP= 0.28 mm,

[XI] *To enhance the readability of this paper, we inverted the need threat scores (in the original scale a high need threat score indicated low need threat), which explains the negative need threat scores in Figures 2 and S2*

field of view= 220). The two first volumes were discarded to allow for equilibration of T1 saturation effects. After the functional run, high-resolution T2-weighted images and high- resolution T1-weighted anatomical images were obtained.

FMRI DATA ANALYSIS

Data were analyzed using Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology, London), version 8, and MATLAB 12.b. Images were corrected for differences in timing of slice acquisition, followed by rigid body motion correction. Preprocessing further included normalization to reorientation of the functional images to the anterior commissure and spatial smoothing with an 8-mm full-width half-maximum Gaussian kernel. The normalization algorithm used a 12-parameter affine transformation together with a nonlinear transformation involving cosine basic functions, and resampled the volumes to 3 mm cubic voxels. Movement parameters never exceeded 1 voxel (<3 mm) in any direction for any subject or scan. Preprocessing of the fMRI time series data used a series of events convolved with a canonical hemodynamic response function (HRF) model. In line with Gunther Moor et al., (2012), BOLD responses were distinguished for events on which participants received (inclusion), or did not receive the ball (exclusion). We divided the inclusion game in three conditions; '*receiving/ not receiving/ playing the ball*', and during the exclusion game, the first two trials where participants received and played the ball once were not analyzed, and all other throws were set as 'not receiving the ball'.

First level models were assessed using general linear model, with modeled events, and a basic set of cosine functions (to high pass filter the data) as covariates. The least-squares parameter estimates of height of the best-fitting canonical HRF for each condition were used in pair-wise contrasts. For all participants, contrasts between conditions were computed by performing one-tailed t-tests, treating participants as a random effect. To examine the effect of social exclusion and inclusion, for all analyses, we compared brain responses using the t contrast: *'exclusion out-inclusion to'*. This contrast has previously been used by Gunther Moor et al (2012), where it was associated with activations in regions commonly associated with Cyberball (i.e. Insula, the ACC, and mPFC). This analysis was also performed as a t-sample t-test to examine differences between the CEM group and the control group.

Next, individual differences were added as predictors in regression analyses. First, we examined whether activation in the contrast *'exclusion out-inclusion to'* was associated with the self-report measurements, using whole brain regression analyses with mood, or need threat scores2 after exclusion (i.e. a higher score indicates a better mood, or high needs threat) as regressors of interest.

In order to examine whether the severity of CEM (see Figure 1) was related to activation in the contrast *'exclusion out-inclusion to'*, we performed

whole brain multiple regression analyses with CEM score as regressor of interest, and physical abuse, physical neglect, and sexual abuse scores as regressors of no interest [XII]. Activations related to other types of maltreatment (e.g. sexual/ physical abuse) during exclusion were examined with a similar whole brain multiple regression analysis, while specifying a specific type of abuse as regressor of interest, and CEM and the other types of abuse as regressors of no interest.

For these analyses, brain activations were first examined at whole brain level with a threshold of P<.005 uncorrected, with a spatial extend K>25 voxels because this threshold and cluster extend have been suggested to provide a good balance between type 1 and type 2 errors (Lieberman & Cunningham, 2009). Because of their presumed role during social exclusion, we then set the entire ACC, mPFC and Insula as Regions of interest (ROIs) (see also Eisenberger, 2012; Meyer et al., 2012). If peak voxel activations fell within these predetermined ROIs, to further protect against Type 1 errors, we also report whether these activations were significant after small volume correction (P_{SVC}) for the spatial extend of the activated region (family wise error at the cluster level). For this SVC we used the automatic anatomical labeling (AAL) toolbox within the Wakeforest-pickatlas toolbox (Maldjian, Laurienti, Kraft, & Burdette, 2003). Brain activations where peak voxel activations fell outside our predetermined ROIs were examined at P<.05 FWE corrected at the whole brain level. All brain coordinates are reported in MNI atlas space. For illustration purposes, we extracted cluster activations (for the main effect of task) using the Marsbar region of interest toolbox (Brett, Valabregue, & Poline, 2002).

BEHAVIORAL ANALYSES

Behavioral responses for the mood and need threat scales were analyzed using Group (CEM, Controls) by measurement moment (Inclusion, Exclusion, Post Scanning) Repeated Measures Analyses of Variances (ANOVAs) in IBM SPSS statistics 19. In addition, the relationship between severity of CEM across participants, and distress (mood and need threat scores) after inclusion, exclusion, and post scanning was assessed using correlational analyses. All analyses were Bonferroni corrected for multiple testing, and significance was set at P<.05 two-sided.

[XII] *We were unable to add diagnosis (yes/no) as regressor of interest in this model, as we only had SCID II data for n=7 controls, and no SCID II data was available for all controls. When we calculated a binary presence vs. absence variable while setting all controls at 0, there was a very high correlation between CEM score and this binary variable (r=.90). Therefore, we choose to examine the impact of Axis I and Axis II diagnosis separately within the CEM group (see Supplement), while focussing on those disorders that are known to impact responses to social exclusion (Current Depression, and Borderline Personality Disorder).*

Results

Impact of social exclusion on self-reported mood and need threat.

A Group (CEM, Controls) by measurement moment (Inclusion, Exclusion, Post Scanning) rmANOVA on mood revealed a main effect of measurement moment on mood score ($F(2,86)=67.47$, $P<.001$), and post-hoc t-tests showed that for both groups mood scores significantly decreased from inclusion to exclusion (t's> 5.58, $Ps<.001$), and significantly increased from exclusion to post scanning (t's<-4.53, $Ps<.001$). In addition, there was a main effect of group ($F(1,43)=6.19$, $P=.02$), and there was a significant mood×group interaction ($F(2,86)=9.52$, $P<.001$). Figure 2 shows that after inclusion, the CEM group reported significantly lower mood scores when compared to controls ($F(1,43)=6.83$, $P=.012$), however after exclusion, this difference disappeared ($F(1,43)=.09$, $P=.77$). At post scanning, the CEM group again reported lower mood feelings compared to controls ($F(1,43)=15.54$, $P=<.001$).

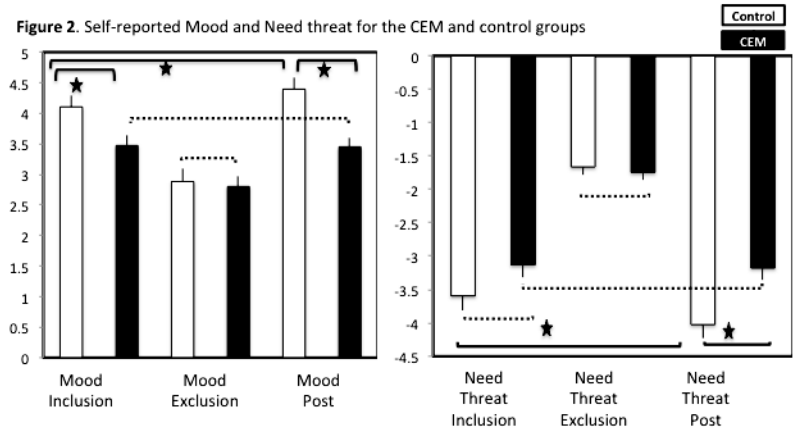
A Group (CEM, Controls) by measurement moment (Inclusion, Exclusion, Post Scanning) rmANOVA on need threat revealed a main effect of measurement moment on need threat scores ($F(2,88)=162.80$, $P<.001$), and post-hoc t-tests indicated that need threat scores significantly increased from inclusion to exclusion in both groups (t's>9.08, $Ps<.001$), and significantly decreased from exclusion to post scanning (t's>-7.80, $Ps<.001$), suggesting that exclusion in the Cyberball task significantly increased threat related feelings across participants. There was a marginal main effect of group ($F(1,44)=3.80$, $P=.06$), and a significant need threat×group interaction ($F(2,88)=8.33$, $P<.001$). Post-hoc tests showed that after inclusion, the CEM group reported similar need threat when compared to controls ($F(1,44)=2.62$, $P=.11$), which remained after exclusion ($F(1,44)=.24$, $P=.62$).

However, at post scanning, the CEM group reported increased need threat feelings when compared to controls ($F(1,44)=9.72$, $P=<.005$), see Figure 2.

Relationship between severity of CEM and self-reported distress (mood and need threat)

Across participants, correlation analyses revealed that the severity of the CEM score was negatively related to mood (r=-.45, $P<.001$) and positively with feelings of need threat (r=.29, $P<.05$) after inclusion. However, after exclusion, no relationships with CEM score and mood, nor need threat were found (r's<-.02, P's>.29). Finally, post scanning, CEM score was again significantly negatively related to mood (r=-.49, $P<.001$) and positively with need threat scores (r=.58, $P<.001$).

Figure 2. Self-reported Mood and Need threat for the CEM and control groups



Note. Significant differences are indicated with an asterisk, whereas dotted lines depict non-significant differences. A high score on the mood scale indicates high mood, whereas a low score on the need threat scale indicates low need threat.

FMRI ANALYSES

MAIN EFFECT OF EXCLUSION>INCLUSION

Across participants, the contrast *'exclusion out-inclusion to'* resulted in activations in the posterior ACC (x=0, y=-36, z=36, K=61, Z=3.43, P<.001, P_{SVC}=.09), and the ventral mPFC (x=-3, y=57, z=-12, K=44, Z=3.51, P<.001), see Figure 3. The activation in posterior ACC marginally survived SVC, but the ventral mPFC area did not survive SVC. All brain regions that were active at the reported threshold (P<.005, K>25) are presented in Table 3. An independent (CEM vs. Controls,) t-test in the same and the reversed contrast revealed no significant group differences.

IMPACT OF CEM SEVERITY ON BRAIN ACTIVATIONS DURING EXCLUSION ACROSS PARTICIPANTS

A whole brain regression analysis across all participants indicated that in the contrast 'exclusion out-inclusion to' the severity of CEM score had a positive association with dorsal mPFC activation (x=-3, y=48, z=33, K=80, Z=3.53, P<.001, P_{SVC} <.05, see Figure 3). Interestingly, both within the control and CEM groups, dorsal mPFC activity in the same cluster was related to CEM severity (see Table S1, Figure S1). There were no significant negative brain activations (see Table 3), nor any brain activations related to physical abuse, physical neglect, nor sexual abuse for the contrast '*exclusion out-inclusion to'*.

BRAIN ACTIVATIONS RELATED TO DISTRESS ACROSS PARTICIPANTS

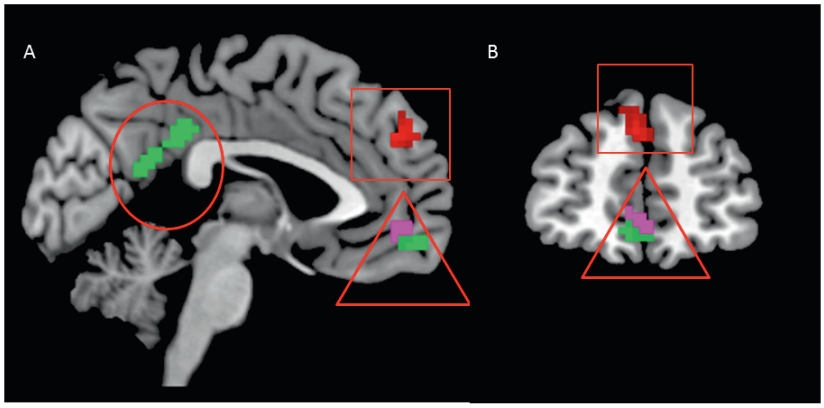
A whole brain regression analysis indicated that need threat scores after exclusion were related to activation in the ventral mPFC contrast 'exclusion out-inclusion to' (x=-3, y=51, z=-6, K=31, P<.001), however, this did not

survive SVC (P_{SVC}=1) (Figure 3). The reversed contrast did not result in any significant differences in brain activation. Additionally, self-reported mood scores after exclusion were not associated with significant brain activations (positively, nor negatively) in the contrast '*exclusion out-inclusion to'*.

CORRELATIONAL ANALYSES BETWEEN DISTRESS AND DORSAL MPFC ACTIVATION

Correlational analyses between activations in the dorsal mPFC cluster (x=-3, y=48, z=33), and self-reported Need Threat revealed a marginal positive relationships after inclusion (*r*=.26, P=.08), but not after exclusion, nor post measurement (*r*'s<.17, P's>.25). Similar correlational analyses revealed that the dorsal mPFC activation was not related to self-reported mood at any of the measurement moments (*r*'s<-.23, Ps>.14).

Figure 3. Brain responses to social exclusion ('*exclusion to-inclusion out*') at x=-3 (A), y=51(B)



Note. The green blobs depict the posterior cingulate (circle), and ventral mPFC cluster (triangle) that were related to social exclusion ('*exclusion to-inclusion out'*) across participants. The violet blob (triangle) depicts the ventral mPFC that was activated in response to need threat at exclusion across participants. The red blob depicts the dorsal mPFC cluster that was related to CEM across participants.

Table 3. Activations for the ' *Exclusion out - Inclusion to* ' contrast at P<.005, K>25.

			K	P FWE	T	Z	P	x,y,z	ROI P SVC
Main effect across participants		Ventral mPFC	44	0.93	3.79	3.51	0.000	-3 57 -12	1.00
				1.00	3.15	2.98	0.001	6 57 -9	
				1.00	2.97	2.82	0.002	-9 45 -9	
		Posterior ACC	61	0.97	3.69	3.43	0.000	0 -36 36	0.09
				0.99	3.52	3.29	0.000	-6 -54 18	
		Inferior frontal gyrus	36	0.98	3.61	3.37	0.000	-42 27 15	
				1.00	3.31	3.11	0.001	-57 24 15	
				1.00	2.98	2.83	0.002	-54 27 6	
Mood exclusion	positive relationship	ns							
	negative relationship	Frontal inferior Opperculum	35	1.00	3.31	3.11	0.001	54 9 27	
Need treat exclusion	positive relationship	ventral mPFC	31	0.92	3.81	3.53	0.000	-3 51 -6	ns
	negative relationship	ns							
CEM vs Controls	CEM> Controls	Superior frontal gyrus	51	0.78	4.04	3.71	0.000	-24 24 51	
				1.00	2.84	2.70	0.003	-36 15 51	
		Angular gyrus	64	0.99	3.53	3.29	0.000	-51 -69 27	
				1.00	3.09	2.93	0.002	-42 -69 36	
				1.00	2.87	2.74	0.003	-33 -78 42	
	Controls> CEM	ns							
CEM severity	Negative	Superior Frontal Gyrus	56	0.71	4.15	3.77	0.000	-18 30 51	
		Dorsal mPFC	80	0.92	3.85	3.53	0.000	-3 48 33	0.05
				0.98	3.62	3.35	0.000	-12 48 42	
				1.00	2.97	2.81	0.002	6 60 30	

DISCUSSION

We examined whether individuals reporting CEM showed enhanced neural responses and emotional distress to social exclusion. We found a dose-response relationship between the severity of CEM and dorsal mPFC responsivity to social exclusion across participants, both in individuals reporting CEM and healthy Controls. Contrary to our expectations, we did not find differences in neural responses to social exclusion when comparing patients reporting moderate to extreme CEM with Controls reporting low to moderate CEM.

Across participants, we found that social exclusion was associated with increases in posterior ACC and ventral mPFC. Although the ventral mPFC response was not significant after small volume correction, ventral mPFC/ACC responsivity to exclusion is reported by numerous studies in adolescents and children (Bolling et al., 2011; Masten et al., 2009; Gunther Moor et al., 2012; Sebastian et al., 2012). Interestingly, the ventral mPFC and posterior ACC have been implicated in a model for self-referential processing (Van der Meer, Costafreda, Aleman, & David, 2010); the posterior ACC is involved in the integration of autobiographical memory with emotional information about the self (Van der Meer et al., 2010). Whereas, the ventral mPFC is assumed to play a role in the more affective components of self-referential processing, through emotional appraisal of self-relevant information and the coupling of emotional and cognitive processing during self-referential processing (Van der Meer et al., 2010). In line with the more affective role of the ventral mPFC, we found that increases in self-reported needs threat after social exclusion (i.e. reduced self-esteem, sense of belonging, meaningful existence, and control) were positively related to ventral mPFC responsivity, albeit at sub-threshold level. Taken together, our findings of posterior ACC and ventral mPFC response during social exclusion

suggest that social exclusion led to negative self- and other referential processing in our sample.

Social exclusion was related to decreases in mood, and increases in needs threat in our sample, which is in line with the idea of enhanced negative self-referential processing related to social exclusion in our participants. The CEM group reported lower mood after inclusion, and at post measurement, yet after exclusion there was no significant difference between the CEM and Control group. In line, the severity of a history of CEM was negatively related to mood after inclusion; however this relationship disappeared after exclusion. These findings may be due to a floor effect in self-reported mood scores, i.e. participants could only rate their distress on a 1-5 scale, and the CEM group already reported lower mood at inclusion, leaving them little space for further reductions. The CEM group also reported higher needs threat at post-measurement, whereas the need threat scores were not significantly different from the control group during in- or exclusion, even though both groups reported an increase in need threat after exclusion. Apparently, need threat feelings were restored at post measurement in the control group, whereas in the CEM group need threat remained relatively high. These findings suggest that, at least for needs threat, the control group seems to recover quicker in the aftermath of social exclusion compared individuals with CEM. Indeed, the severity of CEM was positively related to needs threat after inclusion and at post-measurement. Perhaps, the CEM group is characterized by persistent negative self- and other- referential processing which was present at post-measurement level, and after inclusion. This is in line with findings of our research group that CEM is associated with more negative self-cognitions (Van Harmelen et al., 2010), and more frequent self and other referential processing (i.e. more intrusions of autobiographical interpersonal memories)(Van Harmelen et al., 2011).

We found that the severity of CEM was positively related to dorsal mPFC responsivity to social exclusion. CEM related dorsal mPFC responsivity may reflect a further increase in negative self-and other-referential processing in these individuals, since the mPFC is pivotal in self-referential processing (Blair et al., 2012; Grimm et al., 2009; Lemogne et al., 2009; Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Moran, Macrae, Heatherton, Wyland, & Kelley, 2006; van der Meer et al., 2010; Yoshimura et al., 2009). And a recent meta-analysis suggested that dorsal mPFC responsivity to social exclusion is related to enhanced social uncertainty, social distress, and social rumination (Cacioppo et al., 2013)

Dorsal mPFC in the self-referential processing model (Van der Meer et al., 2010) has been suggested to be important for the evaluation and decision making of self-and other referential information (the evaluation whether information is relevant to the self). Therefore, our findings suggest that severity of CEM may be associated with a further increase in negative self- and other referential thinking during social exclusion. Perhaps individuals reporting CEM perceive social exclusion as especially relevant to themselves. Moreover, negative self- referential processing enhances (negative) bias and

recall, resulting in more frequent, and more intense negative experiences, which in its turn enhances negative self-referential cognitions (Beck, 2008). This is consistent with the slower recovery in the CEM group, and with our previous findings of more negative and more frequent self and other referential processing in CEM (Van Harmelen et al., 2011; Van Harmelen et al., 2010).

The finding of CEM related dorsal mPFC activity is of interest since animal studies utilizing paradigms that closely resemble CEM (e.g. maternal isolation/ separation or isolation rearing) show that the mPFC is particularly affected by early life emotional stress (Arnsten, 2009; Czéh et al., 2007; Lupien, McEwen, Gunnar, & Heim, 2009; McEwen, Eiland, Hunter, & Miller, 2012; Sánchez, Ladd, & Plotsky, 2001; Sanchez et al., 2007). In line, patients and healthy controls reporting CEM show a reduction in dorsal mPFC volume (Dannlowski et al., 2012; Tomoda et al., 2011; Van Harmelen, Van Tol, et al., 2010), and dorsal mPFC hypoactivity during higher order cognitive processing (Van Harmelen et al., under review). Therefore, our findings that individuals reporting CEM show enhanced dorsal mPFC responsivity during interpersonally stressful situations, suggest altered regulation/fluctuations of dorsal mPFC activity in individuals reporting CEM. Perhaps these findings resemble attenuation (mPFC hypoactivity) or increases (mPFC hyperactivity) in negative self- and other-referential processing in these individuals. Future studies should examine this.

Dorsal mPFC responsivity to social stress has been found to be predictive of current, and future depressive symptoms in healthy young adolescents aged 12-14 years old (Masten et al., 2011). However, in our study we did not find that the CEM related dorsal mPFC responsivity was more prominent in our patient sample, nor was it related to a diagnosis of current depression. Across participants, mPFC responsivity was not related to self-reported mood or needs threat (although mPFC responsivity was only related to needs threat in the CEM group). Thus, our findings of CEM related enhanced mPFC responsivity in individuals with CEM may not be related to current (psychiatric) distress. Rather, these findings are more in line with the idea that increased negative self-and other referential thinking (dorsal mPFC) constitutes a vulnerability or sensitivity factor, that may underlie the emotional and behavioral vulnerabilities that have been reported in these individuals (Egeland, 2009; Gilbert et al., 2009). And, only in interaction with other risk factors such as exposure to more recent adverse events, genetic make-up, or low social support, will this vulnerability eventually lead to psychopathology in later life (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van Ijzendoorn, 2011).

The main effects of brain activations related to social exclusion in our sample were relatively weak. This may be related to the fact that we used the contrast *'exclusion out-inclusion to'* in order to calculate brain activations for social exclusion. The CEM group already reported lower mood at inclusion, and we found no reduction in self-reported needs threat, nor

mood in the CEM group when compared to Controls after social exclusion. This suggests that social exclusion in our sample predominantly seemed to cause distress in the control group. In addition, because the CEM group already reported relatively low mood after inclusion, the social exclusion appeared to have a relatively little further impact on self-reported distress within the CEM group. In other words, even though the CEM group may be highly sensitive to social exclusion, they may also be chronically stressed. In that sense, additional social stress may therefore not further increase brain activations related to distress during social exclusion in these individuals. Therefore, including the CEM group when examining overall brain responses related to social exclusion (*'exclusion out- inclusion to'*) in our sample may have led to a reduction in those brain responses. This may also have blurred the overall brain responses to social exclusion.

Finally, contrary to our expectations, we found no group effects on brain activations to social exclusion when comparing the CEM group with healthy Controls. This may be explained by the fact that the CEM group reported moderate to extreme CEM, and the healthy Controls reported low to moderate CEM. Whereas, we found that the severity of CEM showed a positive association with dorsal mPFC responsivity. Therefore, low-moderate CEM in the control group may have reduced our chances of finding group differences, at least in dorsal mPFC responsivity. Moreover, the CEM and Control groups did not show subjective differences in self-reported distress during exclusion, which may have further reduced our chances of finding group differences in brain functioning.

There are some limitations that need to be addressed. First of all, we could not disentangle the effect of current depression from that of history of CEM in our analyses due to high multicollinearity, although current Axis I depressive diagnosis was not related to activations in the dorsal mPFC. And the findings of CEM related dorsal mPFC responses to exclusion were found across participants, and were even apparent in the Control group, suggesting that an Axis I depressive diagnosis might not confound our findings. However, to better disentangle the impact of CEM from the impact of depressive diagnosis on brain functioning during social exclusion, future studies examining patients with depression with and without CEM, and controls with and without a history of CEM are needed.

Second, in our study we assessed CEM retrospectively, and we have to stress the relative subjectivity of self-reported CEM. Furthermore, self-reported CEM may be subject to biased recall. Although, CEM is more likely to be under-reported than over-reported (Hardt & Rutter, 2004). And it should be noted that the test-retest reliability of the CTQ subscales for emotional abuse and emotional neglect have been found satisfactory across different ranges of samples (i.e. college students, psychiatric patients, and convenience samples) (Tonmyr, Draca, Crain, & Macmillan, 2011). Furthermore, in a large sample of patients and controls, it was found that retrospective recall of CEM was not affected by current mood state (Spinhoven et al., 2010).

CONCLUSION

Taken together, we show that severity of CEM is positively related to dorsal mPFC responsivity to social exclusion in both patients with psychiatric disorders and healthy controls. The dorsal mPFC is vital for self and other-referential processing (Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010; van der Meer et al., 2010). Together with findings of more negative and more frequent self-referential processing in CEM (Van Harmelen et al., 2011; Van Harmelen et al., 2010) and slower recovery in terms of need threat after the social exclusion task, our findings suggest increased dorsal mPFC activity during social exclusion may be related to more negative self- and other-reflective thinking in individuals reporting CEM. Increased negative self-and other referential thinking (dorsal mPFC) enhances vulnerability to the development of psychiatric disorders (Beck, 2008). Therefore, our findings may be important in understanding the emotional and behavioral problems that has been reported in these individuals in adulthood (Egeland, 2009; Gilbert et al., 2009)

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SUPPLEMENT

POST-HOC ANALYSES WITHIN THE CONTROL AND CEM GROUPS

We also performed post-hoc analyses in order to test whether CEM related brain activations were present separately within the CEM group and control groups using a whole brain simple regression analysis with CEM score as regressor per group.

In addition, in the CEM group, 25 out of 26 patients had a current or history of Axis 1 diagnosis of depression (i.e. 16 patients had a DSM-IV axis 1 current depression diagnosis, see Table 2). Therefore, we examined the impact of presence vs. absence of current depression in a separate regression analysis. Using a similar simple regression analyses we also examined the impact of the presence vs. absence of borderline personality disorder, given the fact that rejection sensitivity has been related to borderline personality symptoms (Rosenbach & Renneberg, 2011). Finally, we also examined the impact of medication use on brain functioning during exclusion within the CEM group using a whole brain regression analysis.

All post-hoc regression analyses examined whole brain activations at P<.005, K>25. Because of their presumed role during social exclusion, we then set the entire ACC, mPFC and Insula as Regions of interest (ROIs) (see also Eisenberger, 2012; Meyer et al., 2012). Brain activations where peak voxel activations fell outside our predetermined ROIs were examined at P<.05, FWE corrected at the whole brain level. All brain coordinates are reported in MNI atlas space. The results of these analyses are summarized in Table S1.

CEM RELATED BRAIN ACTIVATIONS TO EXCLUSION WITHIN THE GROUPS

In the control group, CEM score was positively associated in the contrast *'exclusion out-inclusion to'* with activations in the right mPFC (x=21, y=48, z=27, K=346, Z=4.02, P<.001, and left dorsal mPFC (x=-6, y=54, z=39, K=34, Z=3.36, P<.001). Figure S1 shows that this was the same region where we found CEM related activations across participants. Finally, CEM score was also associated with Insula activation in the controls (x=39, y=6, z=-15, K=27, Z=3.26, P<.001). There were no other significant brain activations (see Table S1).

Within the CEM group, CEM score was positively associated in the contrast *'exclusion out-inclusion to'* with activation in dorsal mPFC (x=-9, y=54, z=39, K=28, Z=3.98, P<.001). This is the same region that was also significantly related to CEM score across participants (see Figure S1). There were no other significant brain activations (Table S1).

BRAIN ACTIVATIONS RELATED TO CURRENT DEPRESSION, BORDERLINE PERSONALITY OR MEDICATION USE

A whole brain regression analysis showed that the presence (n=16) vs. absence (n=10) of a current diagnosis of depression in the CEM group was

not associated with any brain activations in the contrast *'exclusion out-inclusion to'*.

A similar whole brain regression analysis revealed that medication use (yes, no) was not associated with significant brain activations in the contrast *'exclusion out-inclusion to'*.

Moreover, a whole brain regression analysis showed that the presence (n=7) vs. absence (n=17) of Borderline personality disorder was associated with activations in the mPFC and caudate in the contrast *'exclusion out-inclusion to'* (see Table S1). However, the very small number of individuals with a BPD diagnosis severely hampers the interpretation of this finding. Moreover, this region did not overlap with the mPFC cluster that was related to CEM, and hence cannot explain these findings (Figure S2).

Table S1. Activations for the ' Exclusion out - Inclusion to' contrast at P<.005, K>25 for the Post-hoc analyses.

					peak			
			K	P FWE	T	Z	*P*	x,y,z
Control group	CEM score	Dorsal mPFC	346	0.64	5.21	4.02	<.001	21 48 27
				0.85	4.81	3.81	<.001	12 63 21
				0.87	4.76	3.78	<.001	6 63 27
		Inferior parietal gyrus	43	0.73	5.05	3.94	<.001	39 -48 42
		Middle temporal gyrus	42	0.95	4.55	3.66	<.001	54 -21 -15
		Inferior frontal gyrus triangu	27	0.99	4.19	3.46	<.001	36 24 24
				1.00	3.50	3.01	0.001	45 21 27
		Temporal middle gyrus	37	1.00	4.14	3.42	<.001	-66 -45 -6
				1.00	3.49	3.01	0.001	-60 -36 -12
		Dorsal mPFC	42	1.00	4.13	3.42	<.001	-6 54 39
				1.00	4.00	3.34	<.001	-12 45 45
				1.00	3.89	3.27	0.001	-9 51 30
		Temporal mid Rechts	57	1.00	4.03	3.36	<.001	51 -45 -6
				1.00	3.48	3.01	0.001	63 -39 -6
		Insula	27	1.00	3.88	3.26	0.001	39 6 -15
		Caudate	33	1.00	3.55	3.05	0.001	-9 15 6
				1.00	3.47	2.99	0.001	3 15 9
CEM group	CEM score	Dorsal mPFC	28	0.52	4.80	3.98	<.001	-9 54 39
	SSRI	Post Central gyrus	30	0.988	3.85	3.36	<.001	-21 -30 60
	Current Depression	ns						
	Borderline	mPFC	128	0.765	4.56	3.79	<.001	-12 48 3
				0.858	4.4	3.68	<.001	-12 57 -3
				0.998	3.72	3.24	0.001	9 51 0
		Caudate	28	0.959	4.12	3.51	<.001	-15 3 15
				0.965	4.09	3.49	<.001	-12 12 12

RELATIONSHIP DORSAL MPFC AND SELF-REPORTED DISTRESS WITHIN THE GROUPS

Within the Control group, there was no significant relationship between this dorsal mPFC activation and self-reported need threat after inclusion, exclusion, or post measurement (*r*'s<.21, P's>.38). Similarly, there was no relationship between dorsal mPFC and self-reported mood after inclusion, and exclusion (*r*'s<.23, P's>.34), however, there was a significant relationship between mood at post-measurement and dorsal mPFC responsivity (*r*=.44, P=.06).

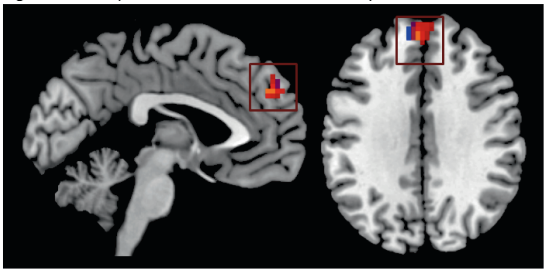
Interestingly, within the CEM group, there was a marginal significant relationship between dorsal mPFC activation and need threat after exclusion

(*r*=.34 P=.09, see Figure S3), but not after inclusion or at post measurement (*r*'s<.21 P's>.31). Furthermore, dorsal mPFC activity was not associated with mood after inclusion, exclusion, or at post measurement (*r*'s<-.19, P's>.35).

Relationship CEM severity and self-reported distress (mood and need threat)

Within the CEM group, CEM score was (marginally) negatively related to mood at all measurement moments (*r*'s>-.37, P's<.06), and positively related to needs threat after exclusion (*r*=.53, P<.005), but not after inclusion and at post measurement (*r*'s<.33, P's>.10). No relationships with CEM score and mood or needs threat were found in the control group (all *r*'s<.37, all P's>.12).

Figure S1. Overlap in MPFC activations for CEM severity.



Note. Figure S1 depicts dorsal mPFC responsivity related to CEM severity across participants (Red), controls (Blue), and patients (yellow). Blurred colours indicate overlap between the regions.

Figure S2. MPFC activations for CEM (circle) and Borderline personality (square).

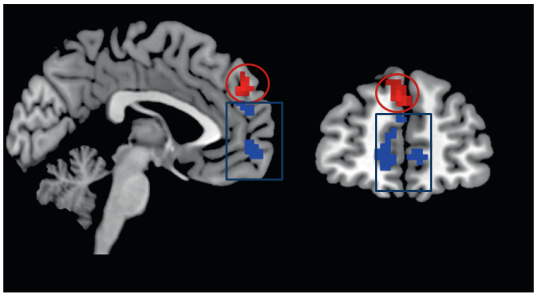
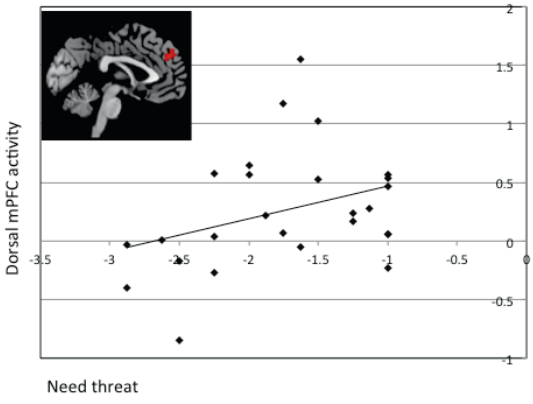


Figure S3. Relationship mPFC and Needs Threat **CEM**

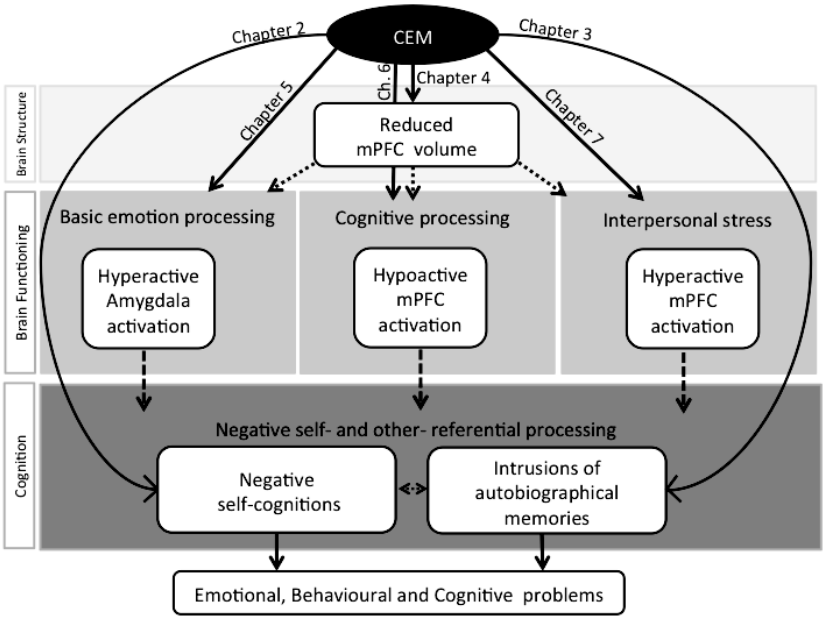


Chapter 8: Summary and Discussion

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

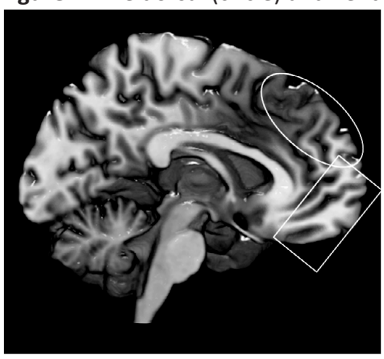
The impact of CEM on brain structure was examined in chapter 4. Using high-resolution T1-weighted 3T MRI anatomical scans and a whole-brain optimized Voxel Based Morphometry approach, we examined whether healthy controls and unmedicated patients with depressive and/or anxiety disorders reporting CEM (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.

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DUTCH SUMMARY

EMOTIONELE KINDERMISHANDELING

Emotionele mishandeling in de kindertijd (psychische mishandeling en/of emotionele verwaarlozing) is de meest voorkomende vorm van kindermishandeling, met prevalentie cijfers tot 36,2% (Stoltenborgh, Bakermans-Kranenburg, et al., 2013). Emotionele mishandeling in de kindertijd vindt grotendeels plaats binnen het gezin (dat wil zeggen 81% van de daders van emotioneel misbruik zijn de ouders (Gilbert, Widom, et al., 2009; Trickett et al., 2009)). Daarom is wel gesuggereerd dat emotionele kindermishandeling het kernelement van een negatieve familie omgeving vormt waarbinnen andere vormen van kindermishandeling ook kunnen plaatsvinden (Hart, Brassard, Binggeli, & Davidson, 2001). Echter, van alle vormen van kindermishandeling is emotionele kindermishandeling de meest verborgen, onder gerapporteerde en minst bestudeerde vorm van kindermishandeling (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). Tot op heden richten de meeste studies zich op de effecten van lichamelijke kindermishandeling en seksueel misbruik (zie Hart & Rubia, 2012; McCrory, De Brito, & Viding, 2012). Deze focus heeft geleid tot uitgebreide kennis over de gevolgen van fysiek en seksueel misbruik van kinderen. Hierdoor is er ook meer aandacht gekomen voor fysiek en seksueel misbruik en de gevolgen daarvan, en zijn er meer en betere interventies ontwikkeld voor personen die dit hebben meegemaakt. De toegenomen maatschappelijke aandacht voor fysiek en seksueel misbruik zou een verklaring kunnen zijn voor de 50% afname in de prevalentie van fysiek en seksueel misbruik van kinderen in de afgelopen 15 jaar in westerse landen (Gilbert, Widom, et al., 2009). Een dergelijke daling is helaas niet waargenomen voor emotionele kindermishandeling. Daarom is het cruciaal om de gevolgen van emotionele mishandeling in de kindertijd te onderzoeken. Om deze reden was het voornaamste doel van dit proefschrift het onderzoeken van de langdurige effecten van emotionele kindermishandeling op cognitie en het brein (d.w.z. de structuur en de werking van de hersenen).

OFFICIELE IDENTIFICATIE VAN EMOTIONELE KINDERMISHANDELING

Emotionele mishandeling wordt door hulpverleners in de jeugdzorg zelden geïdentificeerd als hoofdreden voor zorg (Gilbert, Widom, et al., 2009). Schattingen op basis van het oordeel van professionals ('informant studies') komen neer op een prevalentie van ongeveer 0,3% voor emotionele kindermishandeling (Stoltenborgh et al., 2012). Dit percentage verschilt sterk van prevalenties van emotionele kindermishandeling in zelf-rapportage studies (36,2%) en suggereert dat niet alle personen met een geschiedenis van emotionele mishandeling worden gezien door

zorginstanties. Hulpverleners zien blijkbaar enkel het zogenaamde '*topje van de ijsberg*'. Verder suggereert het verschil in prevalenties tussen zelfrapportage en informant studies dat zorginstellingen en jeugdhulpverleners veel kinderen met emotionele mishandeling niet als zodanig identificeren. Inderdaad, Tricket et al. (2009) beoordeelden gevallen van kindermishandeling die waren gemeld door de Los Angeles County Department of Children and Family Services (DCFS). Volgens de DCFS was 8.9% van bijna 300 kinderen met een gedocumenteerde geschiedenis van kindermishandeling emotioneel mishandeld (d.w.z. verbale mishandeling). Echter, bij gebruik van de definitie van verbale mishandeling zoals gehanteerd door de American Professional Society on the Abuse of Children (APSAC) steeg dit aantal tot 48,4% van de 300 mishandelde kinderen. Verder vonden de onderzoekers dat verbaal mishandelde kinderen meer kans hadden om vaker en meer verschillende soorten van mishandeling te hebben ervaren. Desondanks hadden deze kinderen een kleinere kans om uit huis geplaatst te worden vergeleken met kinderen die lichamelijk of seksueel misbruikt werden (Trickett et al., 2009). De lagere rapportage van emotionele kindermishandeling in vergelijking met fysiek en seksueel misbruik zou kunnen worden verklaard door het feit dat hulpverleners in de jeugdzorg worden ontmoedigd om meer dan één vorm van misbruik vast te stellen (Gilbert, Kemp, et al., 2009; Gilbert, Widom, et al., 2009). Daarbij komt dat emotionele kindermishandeling en de gevolgen daarvan niet zo herkenbaar zijn als die van meer fysieke vormen van kindermishandeling (Egeland, 2009). Een andere reden voor deze onderrapportage van emotionele kindermishandeling door hulpverleners zou kunnen zijn dat er wordt verondersteld dat de effecten van emotionele kindermishandeling minder ernstig zijn dan die van fysiek en seksueel misbruik (Egeland, 2009; Trickett et al., 2009).

DE GEVOLGEN VAN EMOTIONELE KINDERMISHANDELING OP GEDRAG EN EMOTIONEEL FUNCTIONEREN

Emotionele mishandeling in de kindertijd heeft een langdurige negatieve invloed op sociaal gedrag en emotioneel functioneren (Egeland, 2009; Gilbert, Widom, et al., 2009; Rohner, 2004; Wekerle, 2011; Yates & Wekerle, 2009). Verbale mishandeling is bijvoorbeeld gerelateerd aan diverse gedragsproblemen, zoals problemen met impulscontrole, woede, eetstoornissen, auto-mutilatie, suïcidaal gedrag, en alcoholmisbruik (Hart, Bingelli, & Brassard, 1997). Emotionele mishandeling in de kindertijd is ook gerelateerd aan problemen op het terrein van interpersoonlijk functioneren, waaronder hechtingsproblemen, verminderde sociale competentie, seksueel onaangepast gedrag, afhankelijkheid, agressie, geweld, en delinquentie/criminaliteit (Hart, Bingelli, en Brassard, 1997). Bovendien worden personen met een geschiedenis van emotionele kindermishandeling vaker gezien als ondergeschikt, impopulair, meer sociaal teruggetrokken (Egeland, 2009; Shaffer, Yates, & Egeland, 2009; Trickett et al., 2009; Wright,

Crawford & Del Castillo, 2009; Yates & Wekerle, 2009), en hebben ze meer problemen en ervaren meer geweld in de relationele sfeer (Wekerle, 2011). Daarnaast vertonen personen met een geschiedenis van emotionele kindermishandeling meer leerproblemen (Hart et al., 1997), verminderd visuo-spatieel werkgeheugen (Majer, Nater, Lin, Capuron, & Reeves, 2010), minder verbale vloeiendheid, en verminderde cognitieve flexibiliteit (Savitz, Van der Merwe, Stein, Solms, en Ramesar, 2008) en hebben ze in het algemeen een lagere sociaal-economische status (Shaffer et al., 2009). Tenslotte wordt een geschiedenis van emotionele kindermishandeling ook in verband gebracht met lichamelijke problemen, zoals somatische klachten, een slechte lichamelijke gezondheid, en verhoogde mortaliteit (Hart, Bingelli & Brassard, 1997).

EMOTIONELE KINDERMISHANDELING EN PSYCHOPATHOLOGIE OP VOLWASSENHEID LEEFTIJD

Emotionele kindermishandeling is een sterke voorspeller van psychopathologie op latere leeftijd, en in het bijzonder van depressie en angststoornissen in de volwassenheid (Hart et al., 1997; Iffland, Sansen, Catani, en Neuner, 2012; Spinhoven et al., 2010; Wright et al., 2009). Bovendien is emotionele kindermishandeling geassocieerd met borderline persoonlijkheidsstoornis (Hart et al., 1997), ernstigere posttraumatische stress stoornis (Wekerle, 2011) en dissociatieve symptomen (Wright et al., 2009). Vergeleken met fysiek en seksueel misbruik, is emotionele kindermishandeling sterker geassocieerd met depressie en angststoornissen (Iffland et al., 2012; Spinhoven et al., 2010). Tenslotte lijkt het verband tussen fysiek misbruik en depressie en angst op latere leeftijd volledig te kunnen worden verklaard door gelijktijdige blootstelling aan emotionele kindermishandeling (Iffland et al., 2012; Spinhoven et al., 2010). Dit is in overeenstemming met het idee dat emotionele kindermishandeling de belangrijkste component van een negatieve familie omgeving is, waarbinnen andere vormen van misbruik ook kunnen voorkomen.

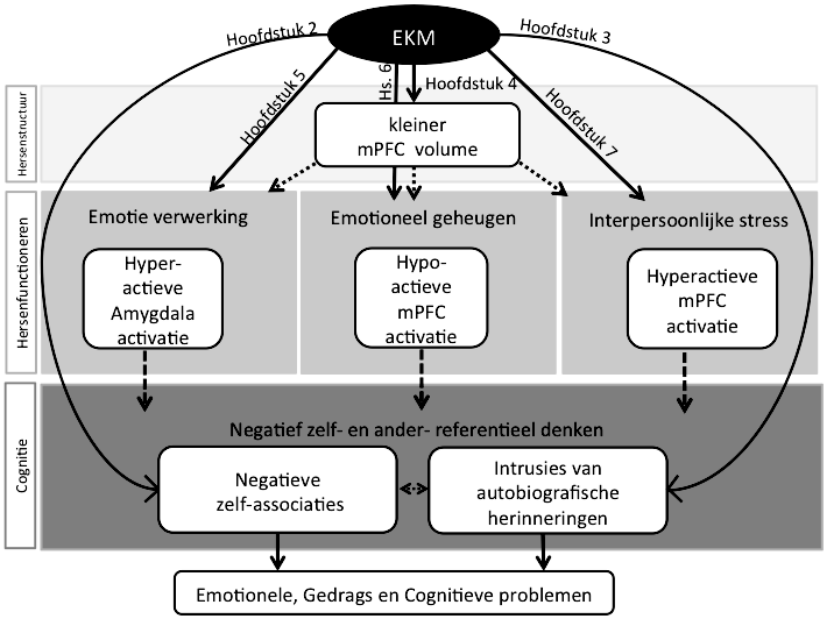
Het is duidelijk dat emotionele mishandeling het risico op het ontwikkelen van psychische problemen kan vergroten, maar het is onduidelijk *hoe* emotionele kindermishandeling kan leiden tot depressieve klachten en angststoornissen op volwassen leeftijd. Het onderzoeken van de verschillende deelprocessen waaruit de etiologische keten bestaat is belangrijk zodat er potentiele targets kunnen worden geïdentificeerd voor therapeutische interventies gericht op personen met een geschiedenis van emotionele kindermishandeling. Een tweede doel van dit proefschrift was daarom om te onderzoeken of de gevolgen van emotionele kindermishandeling op cognitie en het brein gerelateerd zijn aan de ontwikkeling van depressie of angststoornissen. Hiertoe onderzochten we of de gevolgen van emotionele kindermishandeling op cognitie en het brein sterker waren bij patiënten met een depressie en/of angststoornis dan bij personen zonder (geschiedenis van) psychopathologie (hoofdstukken 2,4,5,6,7), en onderzochten we of er een specifieke relatie was tussen de

effecten van emotionele kindermishandeling op cognities en het brein met de ernst van de psychische klachten (hoofdstukken 2, 3 en 7).

DE IMPACT VAN EMOTIONELE KINDERMISHANDELING OP COGNITIES EN HET BREIN

Samenvattend was het primaire doel van dit proefschrift om de lange termijn effecten van emotionele kindermishandeling op cognitie en het brein (structuur en werking) te onderzoeken. Figuur 1 geeft een overzicht van de bevindingen in dit proefschrift.

Figuur 1. Schematisch overzicht van de bevindingen in dit proefschrift.



Noot. De pijlen geven de directe impact van emotionele kindermishandeling (EKM) weer op cognitie (hoofdstuk 2 en 3) en de hersenen (hoofdstukken 4,5,6,7) zoals gevonden in dit proefschrift. De gestippelde pijlen zijn hypothetische effecten die worden verondersteld door de bevindingen van dit proefschrift, maar welke niet expliciet zijn onderzocht. Hs.= Hoofdstuk.

DE GEVOLGEN VAN EMOTIONELE KINDERMISHANDELING OP COGNITIES

In hoofdstuk 2 onderzochten we de relatie tussen emotionele kindermishandeling en impliciete (en expliciete) zelf-depressie en/of zelf-angst associaties onder deelnemers van de Nederland Studie voor Depressie en Angststoornissen (NESDA). De NESDA is een grote longitudinale cohort studie waaraan meerdere universiteiten, academische ziekenhuizen en gezondheidszorginstellingen deelnemen. De NESDA studie is opgezet om het verloop en de gevolgen van depressie en angststoornissen op lange termijn

te onderzoeken. De NESDA studie onderzocht daartoe een breed scala van biologische, psychosociale, emotionele en cognitieve factoren in een zeer grote steekproef (N = 2981; 66,5 % vrouw, leeftijd 18-57) van patiënten met depressie en/of angststoornis, en gezonde controles (zie Penninx, 2008 voor een volledige beschrijving van de studie en de gebruikte methoden). Werving voor de NESDA studie vond plaats in de algemene bevolking, huisartspraktijken en in GGZ-instellingen. Inclusie criteria voor de NESDA studie waren: een DSM-IV diagnose in de afgelopen maand, of in het verleden, van een depressieve stoornis (d.w.z. dysthymie of depressieve stoornis) en/of angststoornis (d.w.z. gegeneraliseerde angststoornis, paniekstoornis met of zonder agorafobie, sociale fobie en/of agorafobie zonder paniekstoornis). Niet-klinische (gezonde) controles zonder huidige stoornis of een verleden van DSM-IV diagnoses werden ook opgenomen in de NESDA studie.

De relatie tussen emotionele kindermishandeling en impliciete (en expliciete) zelf-depressie en/of zelf-angst associaties werd onderzocht omdat impliciete (automatische) zelfassociaties voorspellend zijn voor onmiddellijk affectief gedrag (Engelhard, Huijding, Van den Hout, & De Jong, 2007; Haeffel et al., 2007). Impliciete zelf-associaties zijn simpele associaties in het geheugen die onvrijwillig en automatisch worden geactiveerd (bijv. 'ik=dom'). We onderzochten deze automatische zelf-depressie en zelf-angst associaties met behulp van de Impliciete Associatie Test (IAT; Greenwald, McGhee & Schwartz, 1998). De IAT is een computertaak waarbij door middel van reactiesnelheid de sterkte van zelf-associaties wordt gemeten. Expliciete zelf-depressie en zelf-angst associaties werden gemeten met een vragenlijst. We vonden dat emotionele kindermishandeling was gerelateerd aan verhoogde impliciete (en expliciete) zelf-depressie en zelf-angst associaties. Ook vonden we dat impliciete en expliciete negatieve zelf-associaties beide gedeeltelijk de associatie tussen emotionele kindermishandeling en depressie of angst symptomatologie medieerden.

In hoofdstuk 3 onderzochten we de werking van het autobiografisch geheugen bij gezonde jonge volwassenen (Psychologie studenten) die geen, weinig, matige, of ernstige emotionele kindermishandeling rapporteerden (totaal N = 83). In het verleden is er gevonden dat jong volwassenen die aangeven in hun jeugd emotioneel mishandeld te zijn geweest een meer vermijdende verwerkingsstijl hebben, waarbij ze inhibitie strategieën zoals het onderdrukken van gedachten inzetten om gedachten aan negatieve ervaringen en herinneringen te vermijden (Krause, Mendelson & Lynch, 2003). Helaas blijkt het onderdrukken van gedachten juist contraproductief te zijn; men gaat paradoxaal genoeg juist meer aan de negatieve ervaringen denken (Wegner, Schneider, Carter, & White, 1987; Wenzlaff & Wegner, 2000). De ongewild opkomende herinneringen worden ook wel 'intrusies' genoemd, en deze intrusies ontstaan onmiddellijk, of een tijdje na de poging om herinneringen en/of gedachten te onderdrukken (Wenzlaff & Wegner, 2000). In dit onderzoek keken we of jong volwassenen die emotionele kindermishandeling rapporteren ook inderdaad meer intrusies van

herinneringen ervaarden. Om dit te onderzoeken gebruikten we een computertaak waarbij onze deelnemers de opdracht kregen eerst een positieve of negatieve sociale/interpersoonlijke herinnering op te halen, en daarna de opdracht kregen om deze herinnering te onderdrukken (door er niet aan te denken), maar op een knop te drukken als deze herinnering toch omhoog kwam (een intrusie). We onderzochten het aantal intrusies tijdens en onmiddellijk na actieve onderdrukking van een positieve of negatieve interpersoonlijke herinnering. We vonden dat de groepen niet verschilden in de hoeveelheid intrusies tijdens actieve onderdrukking van zowel positieve als negatieve autobiografische herinneringen. Echter, direct *na* actieve onderdrukking vonden we dat individuen die ernstige emotionele kindermishandeling rapporteerden *meer* intrusies rapporteerden van zowel positieve als negatieve interpersoonlijke herinneringen wanneer ze werden vergeleken met hen die geen, weinig, of matige emotionele kindermishandeling rapporteerden. Verder vonden we dat het aantal intrusies van negatieve interpersoonlijke herinneringen positief gerelateerd was aan de mate van algemene psychische klachten.

Samengevat leveren deze hoofdstukken bewijs dat emotionele kindermishandeling is gerelateerd aan negatieve impliciete en expliciete zelf-associaties, en meer frequente intrusies van negatieve en positieve interpersoonlijke autobiografische herinneringen) (zie Figuur 1). Verder vonden we dat negatieve zelf-associaties de relatie tussen emotionele kindermishandeling en depressieve en angst symptomen medieerde (hoofdstuk 2). Ook vonden we dat intrusies van negatieve herinneringen positief gerelateerd waren aan algemene psychische klachten (hoofdstuk 3). Deze bevindingen kunnen een bijdrage leveren aan het verklaren van de problemen in gedrag, emotie en cognitie van personen met een geschiedenis van emotionele kindermishandeling.

DE GEVOLGEN VAN EMOTIONELE KINDERMISHANDELING OP HET BREIN

In dit proefschrift onderzochten we de impact van emotionele kindermishandeling op het brein in de context van de NESDA-MRI (Magnetic Resonance Imaging) studie. De NESDA-MRI studie bestaat uit 301 deelnemers; 235 patiënten met een huidige (afgelopen 6 maanden) DSM-IV diagnose van een depressie en/of angst stoornis en 66 gezonde niet-klinische controles (66% vrouw, leeftijdscategorie: 18-57 jaar) (Penninx et al., 2008). Om de anatomie van het brein te onderzoeken zijn hoge-resolutie T1-gewogen 3T MRI anatomische scans gemaakt. Ook werden er functionele (f) MRI- scans verkregen tijdens emotionele gezicht verwerking en emotioneel geheugen, tijdens cognitief functioneren (d.w.z. visuo-spatiele ordening), en tijdens rust als deelnemers geen taak uitvoerden. In hoofdstuk 4 van dit proefschrift onderzochten we de invloed van emotionele kindermishandeling op de structuur van het brein, en in de hoofdstukken 5 en 6 is de invloed van emotionele kindermishandeling op het emotioneel

functioneren van de hersenen onderzocht (tijdens emotionele gezicht verwerking en emotioneel geheugen).

DE GEVOLGEN VAN EMOTIONELE KINDERMISHANDELING OP HERSENSTRUCTUUR

In hoofdstuk 4 onderzochten we, met behulp van een geoptimaliseerde Voxel Based Morphometry voor het gehele brein, of de hersenen van volwassen controles en patiënten die emotionele kindermishandeling rapporteren (n=84) verschilden van de hersenen van volwassen controles en patiënten die *geen* kindermishandeling rapporteren (n=97). We vonden dat zelf-gerapporteerde emotionele kindermishandeling geassocieerd was met een significante reductie in het volume van de dorsale mediale prefrontale cortex (mPFC), zelfs in de afwezigheid van fysiek en/of seksueel kindermisbruik (Figuur 1). Daarnaast vonden we dat deze volume vermindering in de mPFC onafhankelijk was van het al dan niet hebben van psychopathologie (dus we vonden een aan emotionele kindermishandeling gerelateerde mPFC volume reductie bij mensen met een huidige diagnose maar ook bij gezonde controles).

Onze bevindingen dat emotionele kindermishandeling gerelateerd is aan een verkleining van de mPFC in de volwassenheid repliceert de bevindingen van tal van dierstudies die gebruik maken van paradigma's die sterk lijken op emotionele kindermishandeling, zoals het scheiden van pups van de moeder, of het in isolatie opgroeien van pups (Czeh et al., 2007; Goldwater et al., 2009; Liston et al., 2006 , Sánchez, Ladd, & Plotsky, 2001; Sanchez et al., 2007). Bovendien zijn onze bevindingen ook gerepliceerd bij proefpersonen (Ansell, Rando, Tuit, Guarnaccia, & Sinha, 2012; Dannlowski, Stuhrmann, et al., 2012; Edmiston et al., 2011; Tomoda et al., 2011). Dus, zowel dierlijke als humane studies bevestigen onze bevindingen dat een geschiedenis van emotionele kindermishandeling leidt tot een kleinere dorsale mPFC die zelfs nog 25 jaar na de emotionele mishandeling gevonden kan worden.

Een verkleining in een structuur kan mogelijk geassocieerd zijn met veranderingen in de functies die aan die structuur gerelateerd zijn. Zo is gevonden dat een verkleining van de prefrontale cortex door stress in de kindertijd geassocieerd is met verminderde cognitieve prestaties (waarvan wordt aangenomen dat deze prestaties afhankelijk zijn van prefrontaal cortex functioneren) (Hanson et al., 2012). De mPFC speelt een cruciale rol in emotioneel gedrag, emotie regulatie, zelf en ander-referentieël denken, en stress respons (Etkin et al., 2011; Phillips et al., 2003; Radley et al., 2004). Daarom zou verminderd mPFC volume in personen met emotionele kindermishandeling wellicht ook gerelateerd kunnen worden aan een veranderde werking van deze hersenstructuur, of van aangesloten structuren zoals de amygdala tijdens emotioneel functioneren van de hersenen.

DE GEVOLGEN VAN EMOTIONELE KINDERMISHANDELING OP HET EMOTIONEEL FUNCTIONEREN VAN HET BREIN

VERHOOGDE AMYGDALA ACTIVATIE TIJDENS EMOTIE VERWERKING

In hoofdstuk 5 onderzochten we het functioneren van het brein in personen met een geschiedenis van emotionele kindermishandeling tijdens de verwerking van emotionele gezichten binnen de NESDA-MRI studie. Daartoe onderzochten we amydala en mPFC reactiviteit tijdens het bekijken van gezichten (Boos, Bang, Verdrietig, Gelukkig, Neutraal) en versus een mix van deze emoties ('scrambled') op één gezicht. We onderzochten dit bij gezonde controles en patiënten met depressieve en/of angststoornissen die emotionele kindermishandeling rapporteerden (n = 60), en we vergeleken deze personen met controles en patiënten die geen kindermishandeling rapporteerden (n = 75). In deze studie vonden we dat emotionele kindermishandeling was geassocieerd met verhoogde amygdala activiteit tijdens het bekijken van gezichtsuitdrukkingen in het algemeen, onafhankelijk van psychiatrische status.

Preklinische studies tonen aan dat scheiding van de moeder tijdens de jeugd gepaard gaat met een verhoogde angstreactie bij pups (Feng et al., 2011, Oomen et al., 2010). In lijn met deze dierstudies is een geschiedenis van ernstige verwaarlozing in de kindertijd in verband gebracht met verhoogde amygdala responsiviteit bij het verwerken van emoties in gezichten bij adolescenten (Maheu et al., 2010). Bovendien is in een aantal recente studies ook gevonden dat emotionele kindermishandeling gerelateerd is aan hyperreactiviteit van de amygdala tijdens het bekijken van emotionele gezichten (Dannlowski, Kugel, et al., 2012; Dannlowski, Stuhrmann, et al., 2012; McCrory et al., 2011, 2013). Samengevat suggereren onze bevindingen tezamen met die van andere studies dat emotionele kindermishandeling gerelateerd is aan een langdurige verhoging van amygdala activiteit tijdens het bekijken van negatieve en positieve emotionele gezichtsuitdrukkingen (Figuur 1).

Interessant is dat we in deze studie geen veranderde activatie in de mPFC vonden bij personen met een geschiedenis van een emotionele mishandeling. Dit suggereert dat de amygdala hyper-responsiviteit voor emotionele gezichtsuitdrukkingen bij volwassenen die emotionele kindermishandeling hebben meegemaakt onafhankelijk is van de invloed van de mPFC. Dit is in overeenstemming met bevindingen dat de connectiviteit tussen de mPFC en de amygdala tijdens rust onveranderd is bij personen die emotionele kindermishandeling rapporteren (Van der Werff et al., 2012), en met onze bevindingen van normale mPFC-amygdala connectiviteit tijdens de verwerking van emotionele woorden (van Harmelen et al., in review). Een alternatieve verklaring kan zijn dat abnormaal mPFC functioneren bij mensen met emotionele kindermishandeling alleen kan worden waargenomen bij taken die meer cognitief functioneren vereisen (zie Shin et al., 2006). Onze gezichtentaak

daarentegen vereiste minimale cognitieve inspanning, omdat mensen alleen het geslacht (man/vrouw) van de persoon op de foto moesten aangeven (Reddy et al., 2004).

MPFC HYPOACTIVATIE TIJDENS EMOTIONEEL GEHEUGEN

In Hoofdstuk 6 onderzochten we of emotionele kindermishandeling gerelateerd is veranderingen in activatie van de mPFC tijdens het bekijken en herkennen van positieve, negatieve, en neutrale woorden met behulp van fMRI. Onze steekproef kwam uit de NESDA-MRI studie en bestond uit patiënten met depressie en/of angststoornissen en gezonde controles die emotionele kindermishandeling rapporteerden (n = 96), en patiënten en gezonde controles die geen kindermishandeling rapporteerden (n = 98). We vonden dat emotionele kindermishandeling geassocieerd was met een consistent patroon van mPFC hypoactivatie tijdens het bekijken en herkennen van positieve, negatieve en neutrale woorden (Figuur 1). Deze bevindingen werden niet verklaard door psychopathologie of een kleinere mPFC onder personen die emotionele kindermishandeling rapporteren.

Hypoactieve mPFC responsiviteit bij patiënten en controles die emotionele kindermishandeling rapporteren zou mogelijk kunnen worden verklaard door veranderingen in zelf-referentieël denken, omdat de mPFC cruciaal is voor zelf en ander-referentieël denken (Van der Meer et al., 2010). In overeenstemming met deze hypothese vonden we dat individuen die emotionele kindermishandeling rapporteren versterkte negatieve zelf-associaties hebben (hoofdstuk 2) en meer frequent nadenken over zichzelf en anderen (d.w.z. intrusies; hoofdstuk 3). Daarom zou de hypoactieve mPFC in individuen die emotionele kindermishandeling rapporteren ook kunnen reflecteren dat deze personen het nadenken over zichzelf en anderen tijdelijk uitschakelen of verminderen om zich te kunnen richten op de emotioneel geheugen taak.

MPFC HYPERACTIVITEIT TIJDENS INTERPERSOONLIJKE STRESS

In hoofdstuk 7 onderzochten we de neurale reacties tijdens interpersoonlijke/sociale stress bij jongvolwassen patiënten en controles die lage tot extreme emotionele kindermishandeling rapporteerden. Deze groep bestond uit 26 patiënten die matige tot extreme emotionele kindermishandeling rapporteerden en die in behandeling waren bij een centrum voor jeugd specialistische geestelijke gezondheidszorg. Ook onderzochten we 20 gezonde controles die aangaven laag tot matige emotionele kindermishandeling te hebben ervaren.

Interpersoonlijke stress werd geïnduceerd met behulp van sociale exclusie door middel van het computerspel 'Cyberball' tijdens fMRI scannen (Williams & Jarvis, 2006). Tijdens Cyberball spelen deelnemers twee spelletjes met een bal met twee andere leeftijdsgenoten (dit zijn echter computer gestuurde 'nep'-deelnemers). Tijdens het eerste balspel worden de deelnemers bij het spel betrokken en ontvangen en gooien ze de bal 1/3 van de tijd. Echter, tijdens het tweede spel ontvangen ze de bal een of

tweemaal in het begin, maar daarna nooit meer. Dit vormt de sociale exclusie. Sociale exclusie tijdens Cyberball gaat gepaard met een vermindering in stemming en zelfvertrouwen en een verhoging van gevoelens van bedreiging (Eisenberger, 2012; deWall et al., 2012).

We vonden dat de ernst van emotionele kindermishandeling positief geassocieerd was met dorsale mPFC responsiviteit voor alle deelnemers tijdens sociale exclusie (Figuur 1). Dit zou mogelijk verklaard kunnen worden door het feit dat sociale exclusie zelf en ander-referentieël denken versterkt (d.w.z. sociale onzekerheid, angst, en rumineren, zie voor een overzicht Cacioppo et al., 2013). Tijdens sociale exclusie vonden we een verhoogde activiteit in de posterieure ACC en ventrale mPFC bij alle deelnemers. Deze hersengebieden zijn betrokken bij een model voor zelf en ander-referentieël denken (Van der Meer et al., 2010). Cruciaal in dit model is dat de dorsale mPFC van belang is voor de evaluatie en de besluitvorming van zelf-en ander referentiële informatie (de beoordeling of er informatie omtrent het zelf relevant is). Daarom kan hyperactiviteit in de dorsale mPFC tijdens sociale stress bij individuen die emotionele kindermishandeling rapporteren worden verklaard door sterker negatief zelf-en ander-referentieël denken bij deze personen. Dit is in overeenstemming met onze bevindingen in hoofdstuk 2 en 3, waar we vonden dat individuen die emotionele kindermishandeling rapporteren meer negatieve zelf-associaties hebben (hoofdstuk 2), en frequenter denken over zichzelf en anderen (hoofdstuk 3).

EEN NEUROCOGNITIEF MODEL VOOR EMOTIONEEL DISFUNCTIONEREN NA EMOTIONELE KINDERMISHANDELING

Op neuro-anatomisch niveau vonden we dat emotionele kindermishandeling was gerelateerd aan een reductie in de grootte van de dorsale mPFC (hoofdstuk 4, Figuur 1). We vonden dat emotionele kindermishandeling ook het functioneren van de mPFC beïnvloedt in hoofdstukken 6 en 7. Verder vonden we dat emotionele kindermishandeling geassocieerd was met een verhoogde reactiviteit van de amygdala, een hersengebied dat veel connectiviteit heeft met de mPFC (hoofdstuk 5). Gedurende een meer basale/automatische werking van de hersenen vonden we dat de amygdala van personen die emotionele kindermishandeling rapporteren hyper-responsief is tijdens het bekijken van emotionele gezichten. Deze bevindingen suggereren dat individuen die emotionele kindermishandeling rapporteren een langdurig verhoogde waakzaamheid vertonen voor de detectie van (negatieve en positieve) emotionele gelaatsuitdrukkingen (hoofdstuk 5). Tijdens meer cognitieve taken vonden we dat emotionele kindermishandeling geassocieerd is met hypoactiviteit in de mPFC tijdens het bekijken en herkennen van emotionele en neutrale woorden (hoofdstuk 6), een taak die door zijn eenvoud weinig cognitieve capaciteiten vereist. Tijdens een meer stressvolle taak (interpersoonlijke stress door sociale exclusie) vonden we aan emotionele kindermishandeling gerelateerde

hyperactiviteit in de mPFC (hoofdstuk 7). Ten slotte vonden we op cognitief niveau dat emotionele kindermishandeling gerelateerd is aan meer *negatieve* zelf-associaties (hoofdstuk 2), en meer *frequente* intrusies van negatieve en positieve interpersoonlijke autobiografische herinneringen (hoofdstuk 3). Deze bevindingen op cognitief niveau, samen met het feit dat de mPFC activiteit erg belangrijk is voor zelf- en ander-referentieël denken (van der Meer et al., 2012) suggereert dat de aan emotionele kindermishandeling gerelateerde mPFC verandering zowel gepaard kan gaan met een verlaging (hypoactiviteit; hoofdstuk 6) als met een versterking (hyperactiviteit; hoofdstuk 7) van nadenken over zichzelf en anderen.

Er wordt verondersteld dat negatief denken over zelf en anderen een centrale rol speelt bij het in stand houden van psychopathologie. Negatief zelf- en ander- referentieël denken kan negatieve gevoelens en cognities versterken en oproepen in nieuwe situaties. Ook kan negatief zelf en ander-referentieël denken herinneringen negatief kleuren (Beck, 2008), wat kan leiden tot meer frequentere en meer intensieve negatieve ervaringen, die op hun beurt het negatieve zelf en ander referentieël denken kunnen versterken. Als gevolg van dit proces kunnen emotioneel mishandelde personen kwetsbaarder worden voor het ontwikkelen en/of in stand houden van depressieve/of angst stoornissen (Beck, 2008). In overeenstemming met dit idee vonden we op een cognitief niveau dat *meer* negatief zelf-referentieël denken (negatieve zelf-cognities; hoofdstuk 2) de associatie tussen emotionele kindermishandeling en depressieve en angstige symptomen medieërt (hoofdstuk 2), en dat het aantal negatieve intrusies van herinneringen sterk positief geassocieerd was met algemene psychische klachten (hoofdstuk 3). Dit komt overeen met bevindingen dat negatieve zelf-cognities voorspellend zijn voor het verloop van depressieve en angststoornissen (Glashouwer, de Jong & Penninx, 2012).

Onze bevindingen suggereren een model waar emotionele kindermishandeling de structuur en het functioneren van de mPFC verandert. Deze veranderingen zouden mogelijk ten grondslag kunnen liggen aan meer negatief en meer frequent zelf en ander-referentieël denken (Figuur 1). Individuen die emotionele kindermishandeling rapporteren zouden misschien in staat kunnen zijn om deze negatieve zelf-en ander referentiële gedachten te verminderen tijdens normaal (niet stressvol) cognitief functioneren (bv geheugen functioneren). Echter, tijdens meer automatische verwerking van sociaal emotionele stimuli (d.w.z. neutrale en emotionele gezichten) en tijdens interpersoonlijke stress gerelateerd aan sociale exclusie zouden ze hier minder adequaat in zijn. De hyperactiviteit van zowel de mPFC en amygdala zouden dan kunnen leiden tot een versterking van negatief zelf- en ander-referentieël denken. Dit zou deze mensen kwetsbaar kunnen maken voor het ontwikkelen van depressie en angststoornissen. Hoewel dit model op dit moment puur hypothetisch is en nog in afwachting van verdere empirische steun, zou dit model kunnen verklaren waarom personen die emotionele kindermishandeling

rapporteren gedrags-, emotionele en cognitieve problemen vertonen in de volwassenheid.

MECHANISMEN WAARDOOR EMOTIONELE KINDERMISHANDELING LEIDT TOT PSYCHOPATHOLOGIE

Het tweede doel van dit proefschrift was te onderzoeken of de aan emotionele kindermishandeling gerelateerde veranderingen in cognitie en het brein zouden kunnen verklaren *hoe* emotionele kindermishandeling leidt tot psychopathologie. In tegenstelling tot onze verwachtingen was het effect van emotionele kindermishandeling op cognitie en het brein niet sterker in de personen met een psychiatrische diagnose. Integendeel, we vonden de versterkte negatieve zelfbeelden, verkleining van de mPFC, de amygdala hyperresponsiviteit, en het veranderde mPFC functioneren zowel in patiënten als in gezonde controles. Dit suggereert dat deze veranderingen in cognitie en het brein geen "*directe route*' vormen waardoor emotionele kindermishandeling noodzakelijkerwijs *altijd* leidt tot de ontwikkeling van depressie en/of angststoornissen. Het is waarschijnlijker dat deze veranderingen kwetsbaarheden vormen en dat deze kwetsbaarheden alleen na blootstelling aan extra 'triggers' (zoals een nieuwe ingrijpende stressvolle negatieve gebeurtenis) leiden tot depressie en/of angststoornissen.

LIMITATIES

Dit proefschrift heeft een aantal limitaties, of zwakke punten, die ik hier zal bespreken. Ten eerste hebben alle studies in dit proefschrift emotionele kindermishandeling gemeten aan de hand van een interview of vragenlijst afgenomen bij volwassenen. Dit retrospectief meten van emotionele kindermishandeling in de kindertijd is subjectief en daardoor gevoelig voor inflatie en vertekening. Zo zouden patiënten met een depressie door hun depressie meer emotionele kindermishandeling kunnen rapporteren, terwijl gezonde controles juist minder emotionele kindermishandeling zouden kunnen rapporteren (McNally, 2003). Uit onderzoek blijkt echter dat emotionele kindermishandeling eerder *minder* dan meer frequent wordt gerapporteerd wanneer het retrospectief wordt gemeten (Hardt & Rutter, 2004). Ook bleek uit onderzoek in de deelnemers van de NESDA studie dat een huidige stemmingsstoornis de rapportage van emotionele kindermishandeling niet significant beïnvloedt (Spinhoven et al., 2010).

Een tweede punt is dat we in dit proefschrift de invloed van emotionele kindermishandeling vooral hebben onderzocht op overwegend geïsoleerd hersenstructuren zoals de mPFC en de amygdala, terwijl hersenstructuren een onderdeel vormen van grotere hersennetwerken (Alexander - Bloch & Giedd, 2013). Toekomstige studies zouden de impact van emotionele kindermishandeling op de structuur en functie van deze hersennetwerken moeten onderzoeken om ons begrip van de pathofysiologie van psychiatrische stoornissen te kunnen bevorderen (Hulshoff Pol & Bullmore, 2013; Linden, 2012).

Ten slotte hebben we in alle studies van dit proefschrift gebruik gemaakt van een cross-sectioneel design. Daarom kunnen we geen uitspraken doen over de causaliteit van onze bevindingen. Het zou kunnen zijn dat een kleinere mPFC een genetische oorzaak heeft en overgedragen wordt van ouders op hun kinderen. Een genetisch kleinere mPFC zou er dan misschien toe kunnen leiden dat ouders hun kinderen eerder emotioneel mishandelen. Deze alternatieve verklaring is echter niet waarschijnlijk omdat onze bevindingen in overeenstemming zijn met die van experimentele dierstudies die paradigma's gebruiken die erg op emotionele kindermishandeling lijken. In deze experimentele dierstudies werd gevonden dat het scheiden van pups van de moeder, of het in isolatie opgroeien van de pups een negatieve impact heeft op de ontwikkeling van het brein (Czeh et al., 2007; Goldwater et al., 2009; Liston et al., 2006 , Sánchez, Ladd, & Plotsky, 2001; Sanchez et al., 2007).

Conclusie

Dit proefschrift poneert dat emotionele kindermishandeling geassocieerd is met een langdurige verandering in cognitie, hersenstructuur, en hersen functioneren. Verder stelt dit proefschrift dat de negatieve effecten van emotionele kindermishandeling op cognitie en het brein ten minste even sterk zijn als de effecten van fysieke en seksuele kindermishandeling. Deze bevindingen lijken robuust te zijn, aangezien ze gevonden zijn in grote steekproeven van zowel patiënten met depressie en angststoornissen als gezonde personen zonder psychiatrische diagnose. Verder worden onze bevindingen onderbouwd door de bevindingen van experimentele dierstudies (Czeh et al., 2007; Feng et al., 2011; Goldwater et al., 2009; Liston et al., 2006; Oomen et al., 2010; Sánchez, Ladd, & Plotsky, 2001; Sanchez et al., 2007), en van andere humane studies (Ansell et al., 2012; Dannlowski, Kugel, et al., 2012; Dannlowski, Stuhrmann, et al., 2012; Edmiston et al., 2011; Maheu et al., 2010; McCrory et al., 2011; 2013 Tomoda et al., 2011). Deze resultaten vormen een belangrijke eerste stap in ons begrip van de nadelige gevolgen van emotionele kindermishandeling. Verder kunnen onze bevindingen mogelijk verklaren waarom mensen met een geschiedenis van emotionele kindermishandeling gedrags- en emotionele problemen vertonen in hun latere leven, al is meer onderzoek nodig om de precieze link met het ontstaan van psychopathologie te kunnen verklaren.

De resultaten in dit proefschrift dat emotionele kindermishandeling een langdurige negatieve invloed heeft op cognitie en het brein benadrukken het belang van een actieve screening voor emotionele kindermishandeling. Hulpverleners in de jeugdzorg zouden standaard moeten screenen op emotionele kindermishandeling naast fysieke en seksuele kindermishandeling. Ook zouden therapeuten die kinderen en volwassenen met psychische klachten behandelen standaard een geschiedenis van emotionele kindermishandeling moeten uitvragen bij hun patiënten. Verschillende epidemiologische studies hebben aangetoond dat wanneer er sprake is van kindermishandeling, de ernst van de psychische klachten

verband houdt met de ernst van mishandeling. Met name bij kinderen en adolescenten kunnen door vroegtijdig ingrijpen in de gezinssituatie de langdurige gevolgen die in de proefschrift beschreven zijn wellicht worden voorkomen.

Tot slot is het cruciaal dat er meer maatschappelijke bewustwording komt van de nadelige gevolgen van emotionele kindermishandeling op cognitie en het brein. Toegenomen bewustwording van en kennis over dit onderwerp onder de algemene bevolking en onder professionals in de jeugd en volwassen zorg zullen hopelijk leiden tot meer rapportage van emotionele kindermishandeling, en het meer toepassen van interventies voor kinderen en volwassenen met (een geschiedenis van) emotionele kindermishandeling. Potentieel zou een verhoogde maatschappelijke bewustwording van de langdurige en schadelijke gevolgen van emotionele kindermishandeling, net als bij fysieke en seksuele mishandeling (Gilbert et al., 2009), zelfs kunnen leiden tot een afname van de prevalentie van emotionele mishandeling in de kindertijd.

PUBLICATION LIST

SUBMITTED/ UNDER REVIEW

1) **Anne-Laura van Harmelen**, Kirsten Hauber, Albert Boon, Bregtje Gunther Moor, Eveline A.M. Crone, Ph Spinhoven, & Bernet M. Elzinga. Enhanced mPFC reactivity to social rejection in young adult patients and controls reporting childhood emotional maltreatment.

2) **Anne-Laura van Harmelen**, Marie-José van Tol, Nic J.A. van der Wee, Andre Aleman, Philip Spinhoven, Brenda W.J.H. Penninx, Frans Zitman, Andre Aleman, Dick J. Veltman and Bernet M. Elzinga. The neural correlates of emotional memory in adults reporting childhood emotional maltreatment.

3) Nicholas D. Walsh, Tim Dalgleish, Michael V. Lombardo, Valerie J. Dunn, Rosemary Abbott, **Anne-Laura van Harmelen**, Maria Ban, and Ian Goodyer. Differential influence of childhood adversity and psychiatric history on variation on cerebellar and amygdala-hippocampal grey matter volume in adolescents.

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1) **Anne-Laura van Harmelen**, Marie-José van Tol, Liliana R. Demenescu, Nic J.A. van der Wee, Dick J. Veltman, Andre Aleman, Mark A. van Buchem, Philip Spinhoven, Brenda W.J.H. Penninx, and Bernet M. Elzinga. (2013) Enhanced amydala reactivity to emotional faces in individuals reporting childhood emotional maltreatment. Social Cognitive and Affective Neuroscience, 8,362-369.

3) Agnes Moors, Jan de Houwer, Dirk Hermans, Sabine Wanmaker, Kevin van Schie, **Anne-Laura van Harmelen**, Maarten de Schreyver, Jeffrey de Winne and Marc Brysbaert (2013). Norms of Valence, Arousal, Dominance, and Age of Acquisition for 4300 Dutch Words. Behaviour Research Methods, 5, 169-177.

4) **Anne-Laura van Harmelen**, Bernet Elzinga, Rogier A. Kievit, Philip Spinhoven (2011). Intrusions of autobiographical memories in individuals reporting Childhood emotional maltreatment. European Journal of Psychotraumatology, 2, 1-11.

5) **Anne-Laura van Harmelen** (2011). Social Pain (Book review). Newsletter for the International Society for Interpersonal Acceptance and Rejection

6) **Anne-Laura van Harmelen** (2011). The cognitive and neurobiological scars of childhood emotional maltreatment. Newsletter for the International Society for Interpersonal Acceptance and Rejection

7) Rogier A. Kievit, Denny Borsboom, Eric-jan Wagenmakers, Jelte Wicherts, Ruud Wetzels, **Anne-laura van Harmelen** & Helma van den Berg (2011). Maatregel om fraude aan te pakken brengt enkel voordelen met zich mee. [Measures to fight scientific fraud only have advantages.] Volkskrant Online, 16 September

8) **Anne-Laura van Harmelen**, Peter J. De Jong, Klaske A. Glashouwer, Philip Spinhoven, Brenda W.J.H. Penninx & Bernet M. Elzinga (2010).

Childhood abuse and negative explicit and automatic self-associations; the cognitive scars of emotional maltreatment. Behaviour Research and Therapy, 48, 486-494.
9) **Anne-Laura van Harmelen**, Marie-José van Tol, Nic J.A. van der Wee, Andre Aleman, Philip Spinhoven, Brenda W.J.H. Penninx, Frans Zitman, Andre Aleman, Dick J. Veltman and Bernet M. Elzinga (2010). Reduced medial prefrontal cortex volume in adults reporting childhood emotional maltreatment. Biological Psychiatry, 68, 832-838.
10)Durk Talsma & **Anne-Laura van Harmelen** (2009); Procedures and strategies for optimizing the Signal to noise ratio in event related potential data. Brain Signal Analysis. Cambridge, MIT press 205-224. (Book Chapter).

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1) **Anne-Laura van Harmelen**, Kirsten Hauber, Bregtje Gunther Moor, Eveline A.M. Crone, Serge A.R.B Rombouts, Philip Spinhoven, Albert Boon, & Bernet M. Elzinga. Neural correlates of mentalizing in adolescents reporting childhood emotional maltreatment.
2) Mirjam Vermeulen, **Anne-Laura van Harmelen**, Esther E. Meerman, Philip Spinhoven & Bernet Elzinga. 'Enhancing self-esteem through positive self-affirmation in young adults reporting childhood emotional maltreatment'
3) Durk Talsma, **Anne-Laura van Harmelen**, & Jan Theeuwes. 'Rapid Reorienting of Attention As Reflected in an N2pc Event-Related Potential Component'
4) Richard J. McNally, Hannah E Reese, Donald J. Robinaugh, **Anne-Laura van Harmelen,** Stephen Haddad, & Jordan W. Smoller. 'Are short alleles of the serotonin transporter 5-HTTLPR associated with psychiatric distress in adults reporting histories of childhood sexual abuse?'

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BIOGRAPHY

Anne-Laura van Harmelen was born on the 13th of August in 1982 in Hilversum. In 1999 she obtained her HAVO (High school) diploma at RSG 't Slingerbos, Harderwijk, the Netherlands. In 2003 she completed her Bachelors degree in Physical Education at Hogeschool Windesheim, Zwolle, the Netherlands. In 2006 she completed her Bachelors degree in Psychology at the University of Groningen, the Netherlands. In August 2006 she started her Masters studies in Psychology at the University of Oslo, Norway. From January until June 2007 she conducted her Masters research at Harvard University, USA under the supervision of Prof. Richard McNally. In January 2008 she completed her Masters in Psychology (Cum Laude) at the VU University, Amsterdam, the Netherlands. From January until June 2008 Anne-Laura worked as a research assistant at the department of Cognitive Psychology at the VU University, Amsterdam, the Netherlands. In June 2008 she started as a PhD student under the supervision of Prof. Bernet Elzinga, Prof. Philip Spinhoven, and Prof. Brenda Penninx, at the department of Clinical, Health and Neuropsychology at Leiden University, the Netherlands. From December 2011 until April 2012, and from February 2013 until May 2013 she performed part of her PhD at the department of Developmental Psychiatry at the University of Cambridge, UK, under the supervision of Prof. Ian Goodyer (Developmental Psychiatry) and Prof. Tim Dalgleish (Medical Research Counsil, Cognition and Brain Sciences Unit). From June 2013 onward, Anne-Laura works as a Postdoctoral Research Associate at the department of Development Psychiatry, University of Cambridge, UK, under the supervision of Prof. Ian Goodyer.