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Capturing the Long-Term Sequelae of Child Maltreatment: Neurocognitive Alterations, Complex Posttraumatic Stress Disorder and the Impact of Psychotherapy

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ABBREVATIONS

ACC	Anterior cingulate cortex
ACE	Adverse Childhood Experiences
ACTH	adrenocorticotropic hormone
ANOVA	Analysis of Variance
APA	American Psychiatric Association
BDI-II	Beck Depression Inventory II
BOLD	Blood-oxygen-level dependent
BPD	Borderline personality disorder
BSL-23	Borderline Symptom List
CA	Childhood abuse
CAPS	Clinician Administered PTSD Scale
CBT	Cognitive Behavioral Therapy
CEN	Central executive network
CEST	Hybrid version of the classic and emotional Stroop Task
CI	Confidence interval
CM	Child maltreatment
col	color
cPTSD	Complex Posttraumatic Stress Disorder
CPA	Child physical abuse
CPT	Cognitive Processing Therapy
CRH	corticotropin-releasing hormone
CSA	Child sexual abuse
cStroop/CST	classical Stroop Task
CT	Cognitive Therapy
CTQ	Childhood Trauma Questionnaire
DTS	Davidson Trauma Scale
dACC	Dorsal anterior cingulate cortex
DBT	Dialectical Behavior Therapy
DBT-PTSD	Dialectical Behavioral Therapy for Posttraumatic Stress Disorder
dlPFC	Dorsolateral prefrontal cortex

DMN	Default mode network
DOS	Disturbances in self-organization
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSS-4	Dissociation Stress Scale, 4 item version
e.g.	example gratia, for example
EMDR	Eye Movement Desensitization and Reprocessing
EPI	Echo-planar-imaging
eStroop/EST	Emotional Stroop Task
FA	Flip angle
fMRI	Functional magnetic resonance imaging
FDR	False Discovery Rate
FOV	Field of view
FWHM	Cube of voxels of size in x,y,z
FWE	Family Wise Error
GLM	General Linear Model
GMV	grey matter volume
HC	Healthy Controls
HPA	Hypothalamic-pituitary-adrenal
ICD	International Classification of Diseases
ICN	Intrinsic connectivity networks
i.d.	id est, that is
IFG	Inferior frontal gyrus
IPDE	International Personality Disorder Examination
ITQ	International Trauma Questionnaire
LCA	Latent class analyses
LPA	Latent profile analyses
M	Arithmetic mean
MACE	Maltreatment and Abuse Chronology of Exposure Scale
MNI	Montreal Neurological Institute
mPFC	medial prefrontal cortex
MPRAGE	magnetization prepared rapid acquisition gradient echo
MRI	Magnetic resonance imaging
ms	Milliseconds

neg	Negative
neu	Neutral
OFC	Orbitofrontal cortex
OR	Odds Ratio
PE	Prolonged Exposure Therapy
PFC	Prefrontal cortex
PGC-PTSD	Psychiatric Genomics Consortium
PTSD	Posttraumatic stress disorder
rACC	rostral anterior cingulate cortex
RCT	Randomized controlled trial
rmANOVA	Repeated measurement analysis of variance
ROI	Region of interest
SAM	Self-Assessment-Manikin
SCAN	Social cognitive and affective neuroscience
SD	standard deviation
SN	Salience Network
SCID	Structure Clinical Interview for DSM-IV
SMA	Supplementary motor area
TAU	Treatment as usual
TC	Trauma Control
TE	Spin echo time
TIV	Total intracranial volume
TR	Inter-scan repetition time
Tra	Trauma
RT	Reaction Times
vACC	ventral anterior cingulate cortex
VBM	voxel-based morphometry
VI	Variable importance
vlPFC	Ventrolateral prefrontal cortex
vmPFC	Ventromedial prefrontal cortex
vs	versus
WHO	World Health Organization
ZAN-BPD	Zanarini Borderline Personality Disorder Interview

1 THEORETICAL BACKGROUND

For much of history, child maltreatment (CM) was considered as a private rather than a societal concern. In 1889, the British Parliament issued the first law to protect children from maltreatment. After many years in 1962, Kempe et al. (1962) demonstrated in their revolutionary article titled *The battered child syndrome* (Kempe et al., 1962) clinical evidence of CM and emphasized the importance of medical diagnostics in the field of child protection. This led to an increase of awareness of the problem and to an initial organized movement within the medical profession to intervene in cases of CM (Fegert & Stötzel, 2016). In the following section, the scope of the problem of CM will be described. Afterwards the conceptualization, symptomatology, epidemiology and etiology of posttraumatic stress disorder (PTSD) and complex posttraumatic stress disorder (cPTSD) as a new diagnostic entity in the 11th revision of the World Health Organization's (WHO) International Classification of Diseases (ICD-11) will be provided. Following this, research on neurocognitive correlates of CM, including functional and structural brain correlates in patients with PTSD, cPTSD and healthy subjects will be outlined. Afterwards research on psychotherapy to tackle neurocognitive alterations in patients with PTSD and cPTSD will be summarized. From significant gaps in each of these fields of literature, the central research questions will be derived and addressed in the studies presented in chapters 2 to 4.

1.1 Child Maltreatment: Scope of the Problem

On the basis of analyses of community surveys in Europe and around the world, the WHO published prevalence rates of 9.6% for sexual abuse, 22.9% for physical abuse, 29.1% for emotional abuse, 16.3% for physical neglect and 18.4% for emotional neglect (World Health Organization, 2015). With regard to Germany, Witt et al. (2017) published prevalence rates of a representative sample of the general population between 14 and 94 years of age and found prevalence rates of 2.6% for emotional abuse, 3.3% for physical abuse, 2.3% for sexual abuse, 7.1% for severe emotional neglect and 9% for severe physical neglect. It is important to note, that these numbers probably do not represent the true magnitude of the problem, due to a high number of unreported cases. Moreover, estimates vary widely depending on the definitions of CM, age boundaries, the type of CM studied, the coverage and quality of official statistics and the research methods (retrospective vs. prospective reports) (Haugaard, 2000), thus limiting communication across disciplines and complicating efforts to identify, treat, and prevent CM effectively. In order to promote a consistent terminology for different forms of CM, several

efforts have been made to provide a conceptual framework of CM and associated terms (American Psychological Association, 2017; Butler et al., 2017; Leeb et al., 2008; World Health Organization, 2015). According to the Violence Prevention Information System by Butler et al. (2017) which was supported by the WHO, CM is defined by "the abuse and neglect of people under 18 years of age. It includes all forms of physical and/or emotional ill-treatment, sexual abuse, neglect or negligent treatment or commercial or other exploitation, resulting in actual or potential harm to the child's health, survival, development or dignity in the context of a relationship of responsibility, trust or power" (Butler et al., 2017, p.3). Moreover, Butler et al. (2017) distinguish between sexual abuse, physical abuse, emotional/mental abuse and neglect. Physical abuse is defined as "intentional use of physical force against a child that results in, or has a high likelihood of resulting in, harm for the child's health, survival, development or dignity" (p.3). Sexual abuse is defined as "the involvement of a child in sexual activity that he or she does not fully comprehend, is unable to give informed consent to, or for which the child is not developmentally prepared, or else that violates the laws or social taboos of society" (p.3). Psychological/mental or verbal abuse is defined as "the failure of a caregiver to provide an appropriate and supportive environment, including acts that have an adverse effect on the emotional health and development of a child" (p.4). Neglect is defined as "the failure of a caregiver to provide for the development of the child – where the caregiver is in a position to do so – in one or more of the following areas: health, education, emotional development, nutrition, shelter and safe living conditions" (p4).

Notwithstanding, the terms *maltreatment* and *abuse* are often used synonymously in the literature. In this dissertation, the overall term *child maltreatment* was chosen to describe both abuse and neglect. Abuse refers explicitly to acts of sexual and physical abuse.

CM is considered as the most reliable risk factor for psychopathology as it is associated with 45% of all childhood-onset disorders and with 26% to 32.0% of later-onset disorders (Anda et al., 2002; Danese & Tan, 2014; Dube et al., 2003; Felitti & Anda, 2010; Green et al., 2010; Kim & Cicchetti, 2010). CM represents a major risk factor for adult psychopathology (Teicher et al., 2016) such as major depression (Gerke et al., 2018), substance abuse (Rasmussen et al., 2018), personality disorders (Battle et al., 2004), (social) anxiety disorders as well as PTSD (Gilbert et al., 2009). Several studies compared prevalence rates of mental disorders in individuals with a history of CM with individuals without such history. In a study by Fergusson et al. (2008), individuals exposed to child sexual abuse (CSA), had a 2.4 times heightened risk for the development of psychopathological symptoms as compared to individuals who were not exposed to CSA. Regarding child physical abuse (CPA), this factor was estimated to be around

1.5. In an Australian prospective longitudinal study by Cutajar et al. (2010), participants with official CSA records were 3.01 times more likely to meet criteria for a mental disorder and 5.47 times more likely to meet criteria for a personality disorder than controls without experiences of CSA. Moreover, the authors found the most increased risks for Borderline Personality Disorder (BPD) (Odds ratio (OR) = 6.1) substance-associated disorders (OR = 5.9) and PTSD (OR = 5.6). Pérez-Fuentes et al. (2013) assessed CSA in a large national sample of the US population and showed an increased risk in CSA survivors for developing almost all mental disorders with an OR of 3.0 (Pérez-Fuentes et al., 2013). In addition, evidence suggests a *cumulative (dose-dependent)* relationship, with more severe forms of CM, a high frequency and combined occurrence of different types of CM leading to a greater risk of developing a mental disorder (Koenen et al., 2017; Steine et al., 2017). Evidence has emerged that a certain proportion of individuals who were exposed to prolonged and severe traumatization during childhood are more likely to develop a more complex presentation of PTSD. This complex symptom pattern is characterized by more extensive psychological dysfunctions (Karatzias et al., 2018; Maercker et al., 2018), higher levels of psychiatric burden, including higher depression and dissociation levels (Brewin, 2019) and poorer treatment outcome (Cloitre et al., 2011) compared to PTSD patients related to mixed traumatic events (Hyland et al., 2017).

1.2 Complex Posttraumatic Stress Disorder related to Child Maltreatment

1.2.1 Conceptualization and Phenomenology

The risk of experiencing traumatic events, such as struggle for survival, natural disaster, great famine, pandemics and war has always been a part of human life in all cultures and times. In the aftermath of the two world wars, a number of terms were used to describe stress reactions after traumatic war events, such as *combat neurosis*, *war neurosis* and *shell shock* (Crocq & Crocq, 2000). The term *posttraumatic stress disorder* came into use in the 1970s in the USA, as Vietnam veterans began experiencing a host of psychological problems, many persisting upon their return home (Crocq & Crocq, 2000). Thereafter it became aware that survivors with various types of trauma (e.g., torture, robbery, car accidents, sexual and physical abuse) developed similar psychological symptoms. These different clinical observations led to the assumption that there is a common clinical picture of stress reactions after experiencing extreme situations (Maercker, 2013). This was officially recognized in 1980, as the American Psychiatric Association (APA) added the new diagnosis PTSD to the third edition of the Diagnostic and Statistical Manual (DSM-III; American Psychiatric Association, 1980) and

firstly considered that the posttraumatic stress experience does not represent personal weakness but rather a normal reaction to an abnormal event (Gersons & Carlier, 2018). In the DSM-III-R (DSM-III-R; American Psychiatric Association, 1987), PTSD was comprised of three symptom clusters: re-experiencing (e.g., intrusions; emotional distress or physical reactivity after exposure to reminders of the trauma), avoidance (e.g., of trauma-related thoughts, feelings or conversation; emotional numbing) and hyperarousal (e.g., hypervigilance; sleeping disorder). This conceptualization of PTSD was strongly criticized by researchers and clinicians working with individuals who were exposed to repeated and severe traumatic events: "The diagnosis of posttraumatic stress disorder, as it is presently defined, does not fit accurately enough. The existing diagnostic criteria for this disorder are derived mainly from survivors of circumscribed traumatic events. They are based on the prototypes of combat, disaster, and rape" (Herman, 1992a, p.119). Herman firstly proposed a more complex form of PTSD, which capture the wide spectrum of symptoms that follow exposure to repeated prolonged and severe traumatic events such as CA, domestic violence, torture, and captivity (Herman, 1992b). To capture the symptom profile described by Herman (1992b), several other diagnoses have been proposed (Resick et al., 2012): *Disorders of Extreme Stress Not Otherwise Specified* (Roth et al., 1997), *Developmental Trauma Disorder* (van der Kolk, 2005) and P*osttraumatic Personality Disorder* (Classen et al., 2006).

An alternative approach was implemented in the latest revision, the DSM-5 (American Psychiatric Association, 2013) and a number of notable evidence-based revisions to PTSD diagnostic criteria were made. The symptom profile of PTSD is no longer categorized as an Anxiety Disorder, but instead included in a new category, Trauma- and Stressor-Related Disorders, in which symptoms related to the complex concept of PTSD are considered as a part of the core symptom profile of PTSD. This is achieved by introducing the new cluster D of PTSD, by means of diversity of symptoms, severity of symptoms, the presence of a dissociative subtype and comorbid mental disorders (American Psychiatric Association, 2013). A dissociative subtype of PTSD was included in the DSM-5 to catch those patients, who in addition to the core symptoms of PTSD, show significant dissociative symptoms. The dissociative subtype is diagnosed in approximately 15-30% of individuals with PTSD (Lanius et al., 2018). Dissociative phenomena are characterized by alterations in consciousness, such as disengagement (*spacing out*), emotional numbing, memory disturbances, depersonalization (feeling outside of your own body), derealization (feeling as if things around you are unfamiliar or strange) and identity dissociation (feeling as there is more than one person inside you) (Lanius et al., 2018). Although, dissociative PTSD has been shown across different trauma

types, it is particularly associated with chronic, repeated and inescapable exposure to traumatic events particularly in individuals that suffered trauma early in childhood (Vonderlin et al., 2018). In preparation of the ICD-11, several studies have been conducted to determine if individuals with PTSD and various trauma types can be classified to distinct groups (PTSD vs. cPTSD) according to their symptoms and psychological impairments (e.g., Resick et al., 2012). Cloitre et al. (2013) were the first to determine whether different classes could be identified according to the PTSD and cPTSD symptom profiles. Based on latent profile analyses (LPA) and latent class analyses (LCA), they identified three classes of individuals (1) a low symptom class (32% of the sample) characterized by generally low scores on all types of symptoms (2) a PTSD class (32%) showing high scores on core PTSD symptoms, but low scores on symptoms reflecting problems of self-organization, and (3) a cPTSD class (36%), defined by high scores on both core PTSD symptoms and problems of self organization. Using LPA and LCA, similar results were found in several studies and in different clinical and community samples of traumatized individuals with different trauma types. These results support the conceptual coherence and integrity of the cPTSD diagnosis (Cloitre et al., 2014; Elklit et al., 2014; Folke et al., 2019; Haselgruber et al., 2020; Karatzias et al., 2017; Kazlauskas et al., 2018; Kazlauskas et al., 2020; Knefel et al., 2015; Knefel et al., 2016; Liddell et al., 2019; Murphy et al., 2016; Palic et al., 2016; Perkonigg et al., 2016; Sachser et al., 2017; Zerach et al., 2019; for review see, Brewin et al., 2017; Cloitre et al., 2020). Indeed, the ICD-11defines two distinct conditions PTSD and cPTSD, under a general category named *Disorders specifically associated with stress* (Brewin et al., 2017; Karatzias et al., 2018). PTSD is defined by symptoms of (1) re-experiencing of the trauma in the here and now, (2) avoidance of traumatic reminders and (3) a persistent sense of current threat. Besides those core PTSD clusters, cPTSD includes an additional cluster that reflects *Disturbances in self-organization (DOS)* (Bondjers et al., 2019) reflected by: (1) affective dysregulation (increased emotional reactivity, lack of affect, violent outbursts), (2) negative self-concept (feelings of defeat, worthlessness, guilt, or shame) and (3) disturbances in relationships (difficulties in establishing or maintaining relationships with others) (Maercker et al., 2013). These symptom clusters of cPTSD are proposed to be typically associated with severe, repeated and multiple forms of traumatic interpersonal exposure (Cloitre et al., 2013).

1.2.2 Epidemiology

Although, the World Mental Health Surveys found that 70% of the general population cross-national, experience traumatic events during lifetime (with exposure ranging from 29% to 83%

depending on country), only a small proportion develop PTSD (5.6%), with prevalence rates ranging from 0.5% to 14.5% across countries (Benjet et al., 2016; Koenen et al., 2017). In a subsequent study, Liu et al. (2017) showed that this variation was associated with trauma type and that interpersonal trauma (e.g., interpersonal sexual and physical violence) conferred an increased risk for PTSD onset. The U.S. National Comorbidity Study (NCS; NCS-R) by Kessler et al. (Kessler et al., 2005a; Kessler et al., 2005b; Kessler et al., 1995) reported a lifetime PTSD estimate of 6.8%-7.8% after various trauma types. With regard to CM, they found evidence that 39.1%-45.9% of women who reported experiences of CSA developed PTSD, compared to 5.7% of women who develop PTSD after other types of trauma. The conditional probability of developing PTSD after experiencing CPA was as high as 48.5% for women. Epidemiologic studies in Germany have found conditional probabilities of developing PTSD after CM in women to be ranging from 28.8% (Perkonigg et al., 2000) to 35.3% (Maercker, 2013). Building on the ICD-11 concept of PTSD and cPTSD, two epidemiological studies by Karatzias et al. (2018) and Maercker et al. (2018) assessed prevalence rates of both PTSD and cPTSD in the UK, USA, Germany and Lithuania. For the USA, they found a lifetime prevalence of 4.0% for PTSD and a lifetime prevalence of 3.3% for cPTSD. Regarding the German population, the authors did not report lifetime prevalence but a 1.5% one month prevalence rate for PTSD and 0.5% for cPTSD (Maercker et al., 2018), making both studies difficult to compare. Other studies found prevalence rates for PTSD ranging from 2.3 to 3.0 % and for cPTSD ranging from 0.6 und 1.0 % (Hyland et al., 2017; Wolf et al., 2015).

1.2.3 Etiology and Pathogenesis

PTSD is relatively unique among mental disorders because of the great importance placed upon the etiological cause, the traumatic stressor, meaning the mandatory exposure to an event that is considered as *traumatic* (American Psychiatric Association, 2013; World Health Organization, 2019). However, numerous individuals who experience a traumatic event do not develop PTSD (Bryant, 2019). Therefore, considerable efforts have been made to increase the understanding of the etiology and pathogenesis of the disorder.

Early *fear conditioning models* of PTSD proposes that the traumatic event (unconditioned stimulus) leads to an unconditioned response, characterized by fear and arousal. This fear response is suggested to become associated (via fear conditioning) with neutral stimuli (conditioned stimuli) present at the time of trauma (e.g., smell, taste, noise) that in turn can trigger fear and arousal responses (conditioned response) even in the absence of the traumatic event (Pitman et al., 2012; Shin & Liberzon, 2010; VanElzakker et al., 2014). This model has

been extended by the view, that following fear conditioning during trauma exposure, impairments in fear extinction learning may further characterize those who develop PTSD (Careaga et al., 2016; Milad et al., 2009; Rougemont-Bucking et al., 2011).

Moreover, *cognitive models* share the assumption, that alterations in cognitive processing may play a fundamental role in the etiology and maintenance of the disorder, such as the Emotion Processing Theory (Foa & Kozak, 1986), The Cognitive Model of PTSD (Ehlers & Clark, 2000) and the Dual Processing Theory (Brewin et al., 1996).

Almost all *neurobiological models* describe trauma exposure as a form of environmental stress that induces a biological stress response in neuroendocrine/physiological and neurobiological systems. Neuroendocrine research focusses on the hypothalamic-pituitary-adrenal (HPA) axis in order to uncover the dysregulations associated with PTSD. The HPA axis is probably the best-studied neurobiological system in relation to PTSD. With activation of the HPA axis (e.g., in threatening situations), the corticotropin-releasing hormone (CRH) and vasopressin are released in the hypothalamus, stimulating the production of the adrenocorticotropic hormone (ACTH) via the pituitary gland. ACTH stimulates the production and release of glucocorticoids (e.g., cortisol) in the adrenal cortex. Glucocorticoids have a broad physiological spectrum of action, among other things; they lead to the mobilization of glucose from energy stores, increase cardiovascular activity, dampen the immune system and support the organism's short-term adaptation to the stress situation. Glucocorticoids act back on the system via negative feedback loops. The coupling of glucocorticoids to glucocorticoid receptors, leads to the termination of the synthesis and secretion of CRH in the hypothalamus, ACTH in the adrenal cortex and thus the activity in the HPA axis (Holsboer, 2000; Lupien et al., 2009). Glucocorticoid receptors are expressed throughout the brain and can regulate as transcription factors further gene expression. Therefore, they can have long-lasting consequences of the brain regions that regulate their release (DeKloet et al., 2005; Sapolsky et al., 2000). Given the hypothesis that stress or high cortisol concentrations have a detrimental influence on brain development, it is assumed that these changes are particularly significant in brain regions with a high density of glucocorticoid receptors and with longer postnatal maturation processes. The most important structures in this line include parts of the prefrontal cortex (PFC), the hippocampus and limbic brain regions (e.g., amygdala), structures with a prominent role in the pathophysiology of PTSD.

The traditional *neurocircuitry model* first proposed by Rauch et al. (1998) suggested an imbalance between prefrontal and limbic regions during the processing of threat. This imbalance is suggested to be characterized by hypoactivation of the medial prefrontal cortex (mPFC) (including the dorsolateral prefrontal cortex [dlPFC], anterior cingulate cortex [ACC],

ventrolateral prefrontal cortex [vlPFC] and ventromedial prefrontal cortex [vmPFC]), that results in an inability to regulate limbic activity such as in the amygdala. The loss of *top-down* inhibition over *bottom-up* emotional processes is supposed to be one of the main components underlying exaggerated fear response and impaired fear extinction (Hughes & Shin, 2011; Liberzon & Sripada, 2008; Rauch et al., 2006; Shin & Liberzon, 2010). Although the neurocircuitry model has proven useful in understanding the etiology of PTSD, it has been challenged by inconsistent findings (Akiki et al., 2017; Patel et al., 2012).

Others emphasize the role of interacting large-scale brain networks *(triple network model)* when investigating the pathophysiology of PTSD (Menon, 2011; Patel et al., 2012; Selemon et al., 2019). Three intrinsic connectivity networks (ICN) have been identified in the brain as crucial in evaluating higher order cognitive processing: the default mode network (DMN), the fronto-parietal/ central executive network (CEN), and the salience network (SN) (often referred to as the cingulo-opercular network in cognitive task literature). The DMN consists of the posterior cingulate cortex, vmPFC, and medial temporal lobe (including the hippocampus) and has been linked to internal mentation such as self-referential processing, social cognition and autobiographical memory (Lanius et al., 2015). The CEN, is associated with cognitively demanding tasks, goal-directed behavior, and cognitive control of emotions, and is anchored in the dlPFC, encompassing the middle frontal gyrus, precuneus, and parts of the premotor cortex (Menon, 2011). The SN, including the dorsal ACC (dACC), parts of the insula and the amygdala plays a key role in salience detection and emotion processing (Menon, 2011). It has been suggested that these ICNs normally interact in a dynamic and antagonistically manner during cognitive and emotional challenges (Lanius et al., 2015). Alterations in any part of these ICNs have been proposed to lead to dysfunctions in the remaining networks mirrored by an unique constellation of psychopathological symptoms, such as PTSD (Menon, 2011). It has been shown that PTSD is characterized by less activation and weakly interconnected brain areas overlapping with the CEN and the DMN and greater activation of brain regions within the SN (Akiki et al., 2017). This has been linked to the specific symptom profile observed in PTSD, including deficits in cognitive control (CEN), hypervigilance and enhanced threat detection (SN), dissociation, intrusions and an altered sense of self (DMN) (Akiki et al., 2017; Etkin et al., 2019; Harnett et al., 2020; Henigsberg et al., 2019; Lanius et al., 2015; Nicholson et al., 2018; Stark et al., 2015).

It is important to note, that a large number of neuroimaging studies revealed a distinct neurobiological pattern in *dissociative PTSD* that is referred to as two different types of emotion dysregulation in PTSD. The first type is characterized by *under*modulation of emotion, such as

hyperarousal, re-experiencing and flashbacks mediated by a failure of prefrontal regions to inhibit limbic activation, typically seen in patients with common PTSD. The dissociative PTSD subtype is associated with emotional *over*modulation due to increased prefrontal inhibition of limbic brain activity leading to depersonalization and derealization symptoms (Lanius et al., 2018; Lanius et al., 2010).

Research on the role of *genetics* in relation to the development of PTSD through twin studies, candidate gene studies, genome-wide association studies (GWASs), methylation and expression studies have made significant progress in the last decade (Olff et al., 2019). Early twin studies estimated the heritability of PTSD to be in the range of 30–72% (Hawn et al., 2019). Advances in molecular genetic research, using both candidate gene and GWAS, have implicated a number of specific variants and quantified the molecular heritability of PTSD. The Psychiatric Genomics Consortium-PTSD Group (PGC-PTSD) combined data from 60 multi-ethnic cohorts and achieved a sample size of 206.655 participants with 32.428 PTSD cases. The research group found substantial SNP-based heritability (i.e., phenotypic variation explained by genetic differences) at 5–20%, which is similar to that for major depression (Nievergelt et al., 2019). Moreover, a genome-wide significant association involving genes related to dopamine and immune pathways have been found to be associated with PTSD, such as *PARK2*, a gene related to Parkinson's disease involved in dopamine regulation (Nievergelt et al., 2019; Sheerin et al., 2017). Recent studies have elucidated how functional genetic variants interact with environmental events (e.g., CM) and have found significant latent gene-by environment (GxE) epigenetic effects for PTSD (Hawn et al., 2019). One gene that has received significant interest in this context, is the FK506 binding protein 51 (*FKBP5*) a key gene within the stress response system that is discussed to increase the risk for PTSD (Binder, 2018). Specifically, it is suggested with the combination of the presence of inherited genetic risk (i.e., the presence of the risk allele for the FKBP5) and trauma exposure, a reduction in DNA methylation occurs at FKBP5. This reduction is supposed to disrupt the homoeostasis and may results in lasting alterations of the neural circuits related to stress regulation (for further information see, Binder, 2018; Watkins et al., 2016). Next to FKBP5, studies have investigated polymorphisms in further HPA-related genes such as *ADCYAP1R1, CRHR1* and *NR3C1*. A recent meta-analysis found the most robust findings for the FKBP5 and NR3C1 in risk for PTSD (Sheerin et al., 2020).

Research regarding the characterization of specific *neurocognitive correlates* of cPTSD and potentially common or unique pathways involved in the pathogenesis and etiology of cPTSD in comparison to PTSD is still in a very early stage. In a review by Lanius et al. (2011) the authors outlined the importance of using a social cognitive and affective neuroscience (SCAN)

approach in understanding the psychology and neurobiology of cPTSD. The authors emphasize deficits related to emotional/self-awareness, emotion regulation, social emotional processing and self-referential processing together with impairments in a core set of brain regions that are supposed to mediate these psychological dysfunctions, such as the cortical midline structures, the amygdala, insula, posterior parietal cortex and temporal poles (Lanius et al., 2011). One has to keep in mind that a clear distinction has to be made between CM-related PTSD and cPTSD because survivors of CM may also develop PTSD without complex PTSD symptoms. Nevertheless, especially high rates of cPTSD symptoms has been found in PTSD patients with a history of prolonged and severe CM (Marinova & Maercker, 2015). Consequently, research of PTSD patients with a history of CM compared to PTSD patients with traumatic events during adulthood (adult-trauma), as well as healthy individuals with and without traumatic experiences may therefore provide some insight into biological pathways of interest to focus on in cPTSD patients.

1.3 Capturing Neurocognitive Correlates of Child Maltreatment in Individuals with and Without (Complex) Posttraumatic Stress Disorder

Numerous studies have demonstrated that individuals with a history of CM with and without PTSD show impairments in different aspects of cognitive control (Bomyea et al., 2020; Cowell et al., 2015; DePrince et al., 2009; Gould et al., 2012; Kavanaugh et al., 2017; Masson et al., 2016; McCrory et al., 2017; Nikulina & Widom, 2013; Scott et al., 2015). However, dysfunctions in cognitive control to inhibit automatic responses and gating distraction especially in the context of emotion seem to be particularly relevant in PTSD (Vasterling & Hall, 2018). These cognitive impairments in PTSD have been discussed to be mirrored in functional as well as structural brain alterations (whereby the temporal relationship is not clear at all) that in turn may contribute to an increased risk for developing PTSD (for reviews see, Aupperle et al., 2012; Cross et al., 2017).

1.3.1 Cognitive Control in the Context of Emotion

Cognitive control or *executive control* (both terms are frequently used interchangeably in the literature) comprises a variety of distinct processes that include updating of working memory, cognitive flexibility, attention shifting, error monitoring, maintenance of attention, updating of working memory, and conflict monitoring or inhibition (Banich et al., 2009; Miyake et al., 2000). Cognitive control is necessary for the flexible allocation of mental resources in the service of goal-directed behavior that involves the inhibition of automatic and predominant (but

no longer required) responses to a situation to respond in a goal-driven manner (Mackie et al., 2013; Posner & Snyder, 1975; Song et al., 2017). Cognitive control has been extensively studied using the classical Stroop (cStroop) (MacLeod, 1991; Stroop, 1935), Simon (Simon et al., 1971), Flanker (Eriksen & Eriksen, 1974) and Go/No-Go (Verbruggen & Logan, 2008) tasks. Reaction times to a target stimuli measured across these tasks are typically slower and less accurate when the stimulus and response are incongruent (e.g., *BLUE* printed in red) as in comparison when they are congruent (e.g., *BLUE* printed in blue), i.e., an *interference effect* (Chen et al., 2018). Stimuli in those purely cognitive paradigms are designed to be absent of emotion. Effects of emotional information are assessed by contrasting neutral stimuli to emotional stimuli, such as emotionally-salient stimuli that may potentially signal danger (Song et al., 2017). In the Emotional Stroop (eStroop) task, participants are presented, next to neutral words, with emotional words and are required to indicate the color of the word while ignoring the distracting effect of the emotional word label. Reaction times are typically longer for emotionally charged words compared to neutral words. This eStroop effect differs from inherent semantic or response conflict occurring for incongruent trials in the standard cStroop task (e.g., *RED* written in blue). The eStroop effect rather reflects that emotionally charged words tend to attract attention, especially when they are relevant to the individual's history (e.g., the word *RAPE* in victims of sexual violence), resulting in a more intense emotional interference, i.e., *emotional interference effect* (Okon-Singer et al., 2015; Pessoa & Ungerleider, 2004; Song et al., 2017). From an evolutionary point of view, the fact that emotional stimuli capture one's attention is favorable: It enables the individual to react selectively and spontaneous to threatening environmental cues. However, this mechanism can become disadvantageous, when the processing of emotional but extraneous stimuli comes at the expense of goal-directed behaviors (Iordan et al., 2013).

1.3.2 Functional Brain Correlates of Cognitive Control in the Context of Emotion

The neural correlates underlying the influence of cognitive control on emotional interference were a widely discussed topic in the last decade. In contrast to a long tradition of research, suggesting that *cold* higher order dorsal cognitive systems and *hot* affective ventral emotional systems do operate independently (e.g., Dolcos & McCarthy, 2006; Iordan et al., 2013), more recent models consider a shared neural circuitry underlying intact cognitive control during emotional challenge to function as a *common core* recruited across diverse cognitive challenges (McTeague et al., 2017). Critical brain regions underlying cognitive-emotional conflict resolution comprise the dACC and bilateral insula as part of the broader SN, together with the

mid-cingulate cortex (extending into pre-supplementary motor area), in conjunction with the dlPFC (extending from middle frontal gyrus to inferior frontal junction/gyrus) and inferior parietal cortex as part of the CEN/fronto-parietal network (for meta-analyses see, Chen et al., 2018; Cromheeke & Mueller, 2014; Feng et al., 2018; McTeague et al., 2017; Song et al., 2017; Xu et al., 2016).

1.3.3 Functional Brain Correlates of Cognitive Control in the Context of Emotion in Posttraumatic Stress Disorder related to Child Maltreatment

Given the case, that emotional stimuli capture one`s attention (emotional interference effect), efficient cognitive control to reduce emotional interference is crucial to complete task-related goals as well as daily work (Iordan et al., 2013) and is considered to be a core capability to ensure mental health (Cisler & Olatunji, 2012; Taylor & Liberzon, 2007). In turn, the inability to inhibit emotional or cognitive responses towards emotional distracters with high valence, characterizes a variety of mental disorders, such as anxiety-, depressive- and addictive disorders as well as PTSD (Chen et al., 2018; McTeague et al., 2017). Several studies using Stroop-type paradigms, have repeatedly demonstrated increased emotional interference in PTSD patients, especially when challenged with trauma-related stimuli (compared to neutral stimuli) when compared to healthy individuals with a history of CM (Trauma Controls; TC) and without CM history (Healthy Controls; HC) (e.g., Bremner et al., 2004; Cassiday et al., 1992; El Khoury-Malhame et al., 2011; Foa et al., 1991; Joyal et al., 2019; McNally et al., 1990; Thomaes et al., 2012; Vrana et al., 1995). However, a few studies did not find evidence for increased emotional interference in PTSD samples compared to TC (Cisler et al., 2011) and HC groups (Kimble et al., 2009). Nevertheless, a greater amount of studies point to increased emotional Stroop interference in PTSD during the processing of emotional and trauma-related stimuli compared to TC and HC samples (for a recent meta-analysis see, Joyal et al., 2019).

An amount of studies investigated the neurobiological correlates of cognitive-emotional dysfunctions in individuals with and without PTSD. Impaired cognitive control in the context of emotional challenge is mostly discussed to be reflected by dysfunctions to adequately activate prefrontal brain regions (e.g., vmPFC, dlPFC) within the CEN in order to regulate limbic brain activation (e.g., amygdala, insula) (Fani et al., 2019). A recent review highlighted the role of the amygdala, insula and dACC as important nodes in the salience system, suggesting that alterations may contribute to PTSD psychopathology (Sheynin & Liberzon, 2017).

In this regard, one of the most replicable findings in fMRI studies of PTSD refers to increased amygdala activity across different task paradigms in comparison to TC and HC groups (for

reviews see, Fitzgerald et al., 2018; Henigsberg et al., 2019; Sheynin & Liberzon, 2017; Stark et al., 2015). As the amygdala region is highly involved in emotional processes, such as salience detection (especially stimuli associated with danger) it is reasonable to assume that hyperactivity in this system may potentially place an individual at greater risk of developing maladaptive behaviors (McCrory et al., 2017). In fact, there is evidence that hyperactivity of the amygdala to threatening stimuli may predict the likelihood of future psychopathology, such as PTSD (Cross et al., 2017). However, TC groups were also shown to exhibit increased amygdala response in comparison to HC groups (Dannlowski et al., 2012; Teicher et al., 2016). Therefore, it is not completely clarified if increased amygdala response to supposedly threatening stimuli is a result of the trauma or a pre-trauma (vulnerable) feature. Nevertheless, a meta-analysis by Stark et al. (2015) that separated studies by type of control group, (PTSD vs. TC vs. HC) found changes in activity in the amygdala and parahippocampal cortex to distinguish PTSD from both control groups (Stark et al., 2015). With regard to the anterior insula, an amount of studies have found increased activation in PTSD patients across different emotional and cognitive paradigms compared to TC groups (for review see, Akiki et al., 2017; Fitzgerald et al., 2018). As already mentioned, the anterior insula is considered to be involved in cognitive-emotional network interactions and may be important for effective modulation of attention in the presence of emotional stimuli during executive control tasks (Akiki et al., 2017; Smith et al., 2014). Exaggerated insula activation when challenged with emotional stimuli has further been considered to specifically contribute to states of emotional *under*modulation, including hypervigilance, re-experience and hyperarousal symptoms (Fitzgerald et al., 2018; Lanius et al., 2015).

A number of studies have found results of increased activation of the dACC in PTSD patients, with higher dACC activation found in PTSD compared to TC groups (for meta-analysis see, Patel et al., 2012) and HC groups (for meta-analysis see, Stark et al., 2015). Higher dACC activation in PTSD is considered to reflect greater response conflicts that might increase cognitive resources in the face of emotional stimuli during cognitive demands (Xu et al., 2016). Moreover, as a part of the SN, increased dACC activation in PTSD patients during cognitive-emotional tasks have further discussed to reflect a state of high arousal and attention that is specifically caused by emotional information (Hayes et al., 2012a). This hyperactivation within regions of the SN is suggested to be accompanied by hypoactivation within the CEN leading to cognitive and executive dysfunctions. Likewise, several studies have repeatedly found decreased activation in PTSD patients compared to TC and HC groups in dorsal, lateral and ventral PFC regions in response to emotional stimuli when engaged in cognitive tasks (for

reviews see, Akiki et al., 2017; Brown & Morey, 2012; Henigsberg et al., 2019; Lanius et al., 2015; Selemon et al., 2019).

An opposite pattern has been found in individuals with dissociative PTSD, characterized by decreased amygdala and insula activation together with increased prefrontal activation during processing of emotional stimuli (Melara et al., 2018; Nicholson et al., 2018; Puetz et al., 2016). This pattern has been associated with emotional *over*modulation involving depersonalization and derealization due to excessive mPFC regulatory activation of limbic regions (Lanius et al., 2018; Lanius et al., 2015; Lanius et al., 2010; Melara et al., 2018; Nicholson et al., 2017; Nicholson et al., 2020; Nicholson et al., 2018).

Studies investigating patients with PTSD related to CM have also found a different pattern of results. Using the eStroop, Bremner et al. (2004) observed increased dACC activation with decreased rostral ACC (rACC) and posterior insula activation in patients with CM related PTSD compared to a TC group. Fonzo et al. (2016) found greater dlPFC activation in response to negative stimuli in PTSD patients after CM compared to TC individuals. However, no significant differences in amygdala activation were observed. Two studies in adolescents who had been exposed to CM, used similar versions of a stop-signal paradigm and found increased activation in brain regions associated with cognitive control, including the dACC and lateral frontal regions during cognitive shifting and inhibitory responses (Carrion et al., 2008; Mueller et al., 2010).

It is possible that differences in PTSD samples (adult-trauma PTSD vs. PTSD related to CM) and differences in comparison groups (TC vs. HC) account for these divergent findings.

1.3.4 Structural Brain Correlates of Posttraumatic Stress Disorder related to Child Maltreatment

Interestingly, brain regions involved in cognitive control in the context of emotion, overlap for the most part with regions found to differ structurally in individuals with a history of CM (Teicher & Samson, 2013). Numerous studies have reported decreased grey matter volume in prefrontal regions in individuals with a history of CM, such as in the ACC (Baker et al., 2013; Heim et al., 2013; Thomaes et al., 2010), mPFC (van Harmelen et al., 2010), vmPFC (Morey et al., 2016), dlPFC (Tomoda et al., 2009), orbitofrontal cortex (Hanson et al., 2010) and in the overall cortical grey and white matter (Sheridan et al., 2012).

Moreover, several studies found reduced volume of the hippocampus in TC groups with a history of CM (Dannlowski et al., 2012; for meta-analysis see, Calem et al., 2017), in PTSD patients with CM history (for review see, Ahmed-Leitao et al., 2016) and in PTSD patients

with various trauma types (for meta-analysis see, Logue et al., 2018). The main finding of these meta-analyses is, that bilaterally hippocampal volume reduction is associated with trauma exposure per se independent of PTSD diagnosis, albeit additional hippocampal reduction is further associated with the diagnosis of PTSD compared to the TC group without PTSD. Since the hippocampus has a high density of glucocorticoid receptors, it is highly susceptible to damage from excessive levels of glucocorticoid, such as cortisol (Sapolsky et al., 2000).
However, some studies did not find alterations in hippocampus volume in maltreated individuals with and without PTSD (Landré et al., 2010; Lenze et al., 2008; Pederson et al., 2004; Veer et al., 2015). Interestingly, studies in maltreated children, repeatedly failed to find hippocampus reductions (Carrion et al., 2001; Mehta et al., 2009; Woon & Hedges, 2008), leading to the assumption, that there may be a *silent period* between trauma exposure and neurobiological alterations, with becoming fully discernible in adulthood (Teicher & Samson, 2016). It has further been shown, that amygdala volume is negatively associated with stress and stress-response mechanisms (McEwen et al., 2016; Roozendaal et al., 2009; Zhang et al., 2018). Similar to the hippocampus, the amygdala has a high density of glucocorticoid receptors. Studies in rodents could demonstrate, that exposure to high levels of chronic stress produces corticosterone-mediated spinogenesis and dendritic arborization leading to hypertrophy of the amygdala, which is opposite to the effects of stress in the hippocampus (Yi et al., 2017; Zhang et al., 2019). However, research on amygdala volume in traumatized individuals with a history of CM is controversial (Herzog & Schmahl, 2018). Increased amygdala volume has been reported in children reared up by chronically depressed mothers (Lupien et al., 2011), institutionally reared and severely deprivated children (Mehta et al., 2009), and adult subjects with disturbed attachment bonds as infants (Pechtel et al., 2014). In contrast, smaller amygdala volumes were found among adults after severe forms of CM and diagnoses of BPD (Driessen et al., 2000; Schmahl et al., 2003; Schulze et al., 2016), Dissociative Identity Disorders (Vermetten et al., 2006) and PTSD (Ahmed-Leitao et al., 2016; Logue et al., 2018; Veer et al., 2015).

1.3.5 The Impact of Type and Timing of Child Maltreatment on Structural Brain Correlates of Posttraumatic Stress Disorder

Although a general and cumulative stress (dose-dependent) effect in the development of PTSD and neurocognitive alterations can be assumed, evidence is emerging that the *type* and the *timing* of traumatization have to be considered when investigating the impact of CM on neurocognitive alterations. In order to understand the specific impact of CM types on neural

development, Sheridan and McLaughlin (2014) proposed a dimensional approach - deconstructing CM into at least two underlying dimensions: *active* and *passive* maltreatment (McLaughlin et al., 2019; Sheridan & McLaughlin, 2014). Active maltreatment is characterized by harmful experiences, i.e., physical and sexual abuse (Sheridan & McLaughlin, 2014). Passive maltreatment represents the absence of important cognitive and social inputs, i.e., emotional and physical neglect (Sheridan & McLaughlin, 2014). Most of studies that focused on neglect are those of early deprivation in institutionally reared children. They observed significantly smaller total brain volume (Mehta et al., 2009), reductions in white and gray matter volume (Sheridan et al., 2012) and in cortical thickness (McLaughlin et al., 2014), disruptions in neural connectivity (Stamoulis et al., 2017), function (Herzberg & Gunnar, 2020) and impairments in associated cognitive functions (Almas et al., 2016; Almas et al., 2020; Beckett et al., 2010; Bos et al., 2009). Studies investigating neuronal consequences of abuse, found a negative correlation between abuse and the size of the hippocampal volume in adulthood but not childhood (Andersen et al., 2008; Teicher et al., 2012), the size of prefrontal cortical grey matter (Tomoda et al., 2009), the size of the visual cortex (Tomoda et al., 2012), and the size of the genital representation field of the primary somatosensory cortex (Heim et al., 2013). Studies, that directly compared passive and active maltreatment found reduced volume in the fusiform gyrus and middle occipital gyrus in individuals exposed to passive compared to those exposed to active maltreatment (Everaerd et al., 2016). Moreover, one study point to gender related differences, in terms of an impact of neglect on male hippocampal volume, whereas female hippocampal volume seems to be affected by the exposure of abuse (Teicher et al., 2018). It is important to note that these results have to be interpreted with caution, as the experience of abuse and neglect co-occur at extremely high rates in children and adolescents, making it impossible to conclude that these patterns are specifically the result of one type of trauma (McLaughlin et al., 2012).

Going one step further, the brain is shaped not only by the type of CM encountered during development, but also by timing, referring to when in development an individual is exposed to CM (Teicher & Samson, 2016). Brain structures have been found to undergo a specific developmental pathway, whereby those brain structures with a high density of glucocorticoid receptors and with longer postnatal maturation processes are thought to be especially vulnerable to environmental input (Lupien et al., 2009). Against this background, recent advances have started to examine the differential impact of timing effects of CM on brain development, thus hinting towards sensitive periods. Existing results provide evidence for a sensitive period during 3-5 years and 11-13 years of age, during which hippocampal volume is maximally susceptible

to the exposure of CSA (Andersen et al., 2008). Pechtel et al. (2014) compared a TC group with disturbed attachment and exposure to emotional abuse and neglect with a HC group and found evidence for increased bilateral amygdala volume in the TC group. Regarding timing effects, the authors further identified a sensitive period for the right amygdala during 10-11 years of age, when amygdala volume is maximally susceptible to the exposure of stress (Pechtel et al., 2014). In a longitudinal developmental study by Whittle et al. (2013), the authors demonstrated an initial augmenting effect of CM on amygdala and hippocampus volume development, but a hampered growth of both brain structures over time.

1.3.6 Neurocognitive Correlates of Complex Posttraumatic Stress Disorder related to Child Maltreatment

Data of neurocognitive correlates of cPTSD related to CM are sparse and mostly published by one research group. They found increased activation in the ACC and hippocampus during encoding of negative words (Thomaes et al., 2013; Thomaes et al., 2009) and a trend for increased anterior insula and dACC activation compared with a HC group during processing of neutral words when performing a Stroop task (Thomaes et al., 2012). In a further study the authors investigated structural brain abnormalities in cPTSD patients and found cPTSD patients to have reduced grey matter concentrations in the right hippocampus, right ACC, and OFC compared to HC individuals (Thomaes et al., 2010). In light of these findings, the authors concluded that cPTSD is associated with more sever neural imaging correlates, primarily affecting brain regions associated with cognitive functions and emotion regulation. Moreover, they suggested that structural abnormalities in the brain seem to be more extensive in cPTSD patients compared to PTSD patients who had experienced single trauma (Giourou et al., 2018; Marinova & Maercker, 2015; Thomaes et al., 2015). However, these data are in clear need of replication.

1.4 Targeting Neurocognitive Correlates of Child Maltreatment in Individuals with (Complex) Posttraumatic Stress Disorder

Within the last decades, various psychotherapeutic approaches (next to pharmacological approaches) have been developed for the treatment of PTSD. According to the guidelines for PTSD treatment (American Psychological Association, 2017; International Society for Traumatic Stress Studies, 2019a; Schäfer et al., 2019), treatments of choice for adult patients with PTSD are Trauma Focused Cognitive Therapy including Cognitive Behavioral Therapy (CBT) (Monson & Shnaider, 2014), Cognitive Processing Therapy (CPT) (Resick et al., 2016),

Cognitive Therapy (CT) (Ehlers et al., 2014; Ehlers & Clark, 2000), Prolonged Exposure Therapy (PE) (Foa et al., 2019) and Eye Movement Desensitization and Reprocessing (EMDR) (Shapiro, 2018).

Importantly, meta-analyses demonstrated substantially lower effect sizes of psychotherapeutic treatments in PTSD patients related to CM (g=0.72) (Ehring et al., 2014), when compared to PTSD patients related to mixed traumata (ranging from g=1.08 to 1.40) (Cusack et al., 2016). These results were supported by a recent meta-regression involving 51 randomized controlled trials (RCT), indicating poorer treatment response in individuals with a history of CM (Karatzias et al., 2019). Most psychotherapeutic treatments as summarized above have been developed for PTSD patients who had experienced a traumatic event during adulthood. There has been a very long debate whether these treatments are sufficient for patients with PTSD related to CM and cPTSD, or whether these patients need more specific interventions (De Jongh et al., 2016). In response to the inclusion of cPTSD as a new diagnosis in the ICD-11 (Brewin, 2019), international guidelines recommend phase-based treatments that combine trauma-focused techniques with interventions for emotion regulation and improving disturbances in relationships (American Psychological Association, 2017; International Society for Traumatic Stress Studies, 2019b; Schäfer et al., 2019). An example for a phase-based psychotherapeutic program is Dialectical Behavioral Therapy for PTSD (DBT-PTSD), which has been designed to meet the needs of individuals with a history of CM and complex presentations of PTSD. DBT-PTSD combines interventions of the *classic* DBT treatment (Bohus, 2004; Linehan, 1993) with acceptance and commitment therapy (ACT) and compassion-focused therapy (Bohus et al., 2019). One significant element of DBT-PTSD is the development of *skills*. Skills aim to interrupt and modify automated maladaptive emotions and cognitions as well as behavioral patterns (e.g., dissociation) during extreme experiences of stress and arousal (Bohus et al., 2019). The evaluation of DBT-PTSD has been shown to be highly efficacious in treating cPTSD patients under residential (ranging from g=1.22 to 1.27) (Bohus et al., 2013; Steil et al., 2011) as well as under outpatient condition (Cohen's d = 1.50) (Steil et al., 2018). Next to DBT-PTSD, CPT (Resick et al., 2017) has been shown to be highly efficacious in treating PTSD after various trauma types (for meta-analysis see, Asmundson et al., 2019) as well as in treating individuals with a history of CM (Holder et al., 2019; Rosner et al., 2019). In a recent RCT in cPTSD patients related to CM, Bohus et al. (2020) compared the efficacy of DBT-PTSD against CPT and found significantly improved PTSD symptoms for both treatments (Cohen's d=1.35 for DBT-PTSD and Cohen's d=0.98 for CPT) and a small but significant superiority of DBT-PTSD (group difference: 4.82, [95% CI, 0.67- 8.96], p=.02; d=0.33) (Bohus et al., 2020).

Several studies have investigated the extent to which psychotherapy improves cognitive functions in patients with PTSD (see, Fani et al., 2009; Flanagan et al., 2018; Koch et al., 2019; Vermetten et al., 2003 for psychopharmacological interventions on neurocognitive functions in PTSD). Using an eStroop type paradigm, one study has demonstrated improved eStroop performance in PTSD patients compared to HC individuals after EMDR (El Khoury-Malhame et al., 2011). A further study demonstrated improvements in executive functions after ten sessions of trauma-focused treatment (including CPT and PE) (Walter et al., 2010). However, the sample size in this study was very small (N=10) (Walter et al., 2010). In a recent RCT by Nijdam et al. (2018), the authors examined memory and executive functioning before and after trauma-focused psychotherapy in 88 patients with PTSD (Nijdam et al., 2018). They found that trauma-focused psychotherapy improved neurocognitive functioning in verbal learning and memory as well as information processing speed and executive functioning (Nijdam et al., 2018). Other studies, however, have not found effects of psychological treatment on executive functioning in PTSD (Devineni et al., 2004). Due to the small number of studies, additional research is necessary to determine what types of treatments may confer benefits to cognitive functions in patients with PTSD.

In order to identify neurobiological correlates of psychotherapeutic treatment, longitudinal fMRI studies aim to investigate neurocognitive measures before and after psychotherapy. Next to longitudinal studies, prediction studies using fMRI aim to quantify the probability of future health outcomes based on a set of predictors (for results of prediction studies see, Bryant et al., 2007; Cisler et al., 2015; Falconer et al., 2013; Fonzo et al., 2017a).

Longitudinal studies using trauma-script paradigms showed increased superior and dorsomedial prefrontal gyrus activation, increased dACC and hippocampus activation and decreased amygdala activation after treatment (Levin et al., 1999; Lindauer et al., 2008; Peres et al., 2011; Peres et al., 2007). In a recent study by Abdallah et al. (2019), active military participants with and without PTSD, underwent CPT group therapy or present-centered therapy (PCT) (six weeks and 12 sessions) and were scanned before and after treatment using subject-specific script imagery. Participants in both groups, showed reduced activation within the SN as well as increased activation within the CEN after treatment. Moreover, CPT group therapy was further associated with increased connectivity within the CEN, supporting the idea that CPT affects the CEN in particular and leading to enhanced cognitive control (Abdallah et al., 2019). Using an emotional face paradigm, two studies found that symptom improvement was associated with decreased activity in the hippocampus, ventral ACC (Dickie et al., 2011) amygdala (Felmingham et al., 2007) and with increased rostral ACC activity (Felmingham et al., 2007).

In a study investigating adolescent PTSD patients with physical and/or sexual abuse history, the authors found symptom improvement to be correlated with decreased amygdala and insula activation after treatment (Cisler et al., 2016). Further insight is provided by studies investigating inhibitory control by Stroop and Go/noGo paradigms. Using an Affective Stroop task paradigm, Roy et al. (2010, 2014) found increased dACC activation and decreased amygdala activation following PE therapy for PTSD (Roy et al., 2014; Roy et al., 2010). Aupperle et al. (2013) investigated emotion processing during the anticipation and presentation of emotional pictures in battered women and showed after treatment enhanced ACC and decreased anterior insula (see also, Simmons et al., 2013) activation during anticipation, and decreased dlPFC and amygdala response during image presentation. However, one study has found increased insula activation in response to a trauma-unrelated emotional processing task to be associated with symptom improvement (van Rooij et al., 2016). Fonzo et al. (2017b) examined emotional reactivity and emotion regulation during a cognitive reappraisal task and found treatment-specific changes in fronto-polar brain circuits (increased fronto-polar cortex activity and vmPFC connectivity) during the regulation of negative affect (Fonzo et al., 2017b). A recent study assessed neural correlates of emotion processing and regulation in military veterans with and without PTSD before and after treatment with PE. Results revealed a significant relation between symptom reduction and less recruitment of prefrontal regions during reappraisal of negative emotions after treatment (Joshi et al., 2020).

Thomaes et al. (2012) were the first who studied treatment effects of a cognitive behavioural stabilizing group treatment in addition to treatment as usual (TAU) vs. TAU only in cPTSD related to CM during fMRI. Before treatment, cPTSD patients showed increased activation in the anterior insula and dACC while completing a Stroop-type paradigm. After treatment, patients showed diminished activation in the superior frontal cortex, dACC and insula, with no change in amygdala activation (Thomaes et al., 2012). Even though this study provides first evidence of neurobiological treatment effects in cPTSD after CM, the results are in clear need of replication. Moreover, there is no study investigating neurobiological treatment effects of trauma-focused outpatient treatment over a longer period in this severely affected group of patients with cPTSD related to CM.

1.5 Integration

CM is highly prevalent worldwide and is correlated to higher rates of PTSD than other types of trauma. The development of PTSD in the aftermath of prolonged and severe CM is often associated with clinical features that extend beyond classic PTSD symptoms such as affective

dysregulation, negative self-concept and disturbances in relationships. This complex form of PTSD has been included in the ICD-11 as a new diagnostic entity. Importantly, numerous individuals who experience CM do not develop PTSD, driving researchers to identify factors of vulnerability and/or resilience following exposure to trauma. Building on a large body of studies, contemporary models of PTSD agree that almost all symptoms can be linked to alterations in neurocognitive processing. This includes persistent enhancement of attention to (potential) threatening stimuli (hypervigilance) with impaired cognitive control mechanisms to inhibit emotional and cognitive responses (emotional interference). These alterations were discussed to be associated with heightened activity of limbic regions within the SN and diminished activation in prefrontal regions of the CEN leading to intrusive thoughts, flashbacks and disturbances in emotional regulation. However, studies regarding the characterization of specific neurocognitive correlates of cPTSD and potentially common or unique pathways involved in the pathogenesis and etiology of cPTSD in comparison to PTSD are extremely sparse and published by only one research group. Regarding structural brain correlates of PTSD related to CM, several studies have found volumetric changes in stress and emotion associated brain regions (especially in the amygdala and hippocampus) that are hypothesized to play a pivotal role in individual differences contributing to resilience or vulnerability in the aftermath of CM. Although a cumulative (dose-dependent) effect of CM can be assumed, the role of type and timing of CM has become of particular interest when investigating neurocognitive correlates contributing to psychopathology. Emerging evidence points to sensitive periods and specificity of CM subtypes to differentially impact neurocognitive correlates in individuals with and without psychopathology.

Several psychotherapeutic approaches have been developed for PTSD treatment and have been shown to be successful in treating PTSD symptoms as well as neurocognitive alterations. However, those treatments have mostly been developed for survivors of adult-trauma PTSD. Meta-analyses demonstrated substantially lower effect sizes of psychotherapeutic treatments in PTSD related to CM and cPTSD indicating poorer treatment response. Even though preliminary data point to the effectiveness of psychotherapy on normalizing neurocognitive functions in cPTSD patients, these data are in clear need of replication.

1.6 Aims and Research Questions

The overall aim of this thesis was to examine the long-term sequelea of CM with an emphasis on neurocognitive correlates of CM-related PTSD and cPTSD and the impact of psychotherapy on these measures. In light of the above, the following studies focused on three relevant aspects:

Study I investigated the role of CM and the presence of psychopathology on cognitive control, emotional interference and underlying functional brain correlates. Study II focused on structural brain alterations in individuals with a history of CM with and without cPTSD with an emphasis on type and timing of traumatization. Study III explored whether neurocognitive alterations as measured in study I, can be altered by 12 months of outpatient psychotherapy with DBT-PTSD or CPT.

More precisely, **study I** examined the role of psychopathology and CM history on functional correlates of cognitive control and emotional interference during the cStroop and eStroop task in 28 female patients with cPTSD, 28 female TCs and 28 female HCs. Since one limitation of the previous fMRI studies was the absence of both matched HC and TC groups, the inclusion of both control groups provided us with the opportunity to explore whether neural alterations are associated with cPTSD symptoms or result from the experience of trauma alone. We hypothesized increased interference for trauma-related words (reflected by slower reaction times and increased errors) in the eStroop task in patients with cPTSD compared to both control groups. Based on the aforementioned results, we further expected increased neural activity during emotional (especially trauma-related) words in the amygdala, insula and dACC, as well as decreased activation in the dlPFC and vmPFC.

Study II focused on the effects of CM on structural brain correlates with an emphasis on the influence of trauma type and timing of CM in a sample of 68 individuals exposed to prolonged CM with cPTSD (n= 42) and without cPTSD (TC; n = 26).

In a first step, study II investigated the impact of global CM severity, global abuse and neglect severity on the amygdala, hippocampus and ACC volume as important stress and emotion associated brain regions. Second, building on first evidence of timing effects of CM on amygdala and hippocampus volume (Andersen et al., 2008; Pechtel et al., 2014), study II aimed to replicate those findings. Third, a special focus was on the potential interaction of severity of trauma type and timing of trauma exposure on brain volume.

Study III addressed the question whether behavioral and neural alterations of cognitive control and emotional interference in cPTSD patients as measured in study I can be altered through 12 months of outpatient treatment with DBT-PTSD (Bohus et al., 2019) and CPT (Resick et al., 2016). Based on the results of study I and a comparable study in cPTSD by Thomaes et al. (2012), we hypothesized that patients after 12 months of treatment will show (a) reduced Stroop interference for trauma-related words, reflected in faster reaction times and less errors, (b) decreased activation in target limbic brain regions as in the insula and amygdala and (c) decreased activation in target prefrontal brain regions as in the dACC and dlPFC. Moreover,

we investigated potential treatment-associated neural and behavioral differences between DBT-PTSD vs. CPT by explorative analyses. For an overview of the research structure and the relationship between the experimental studies, see Figure 1.1.

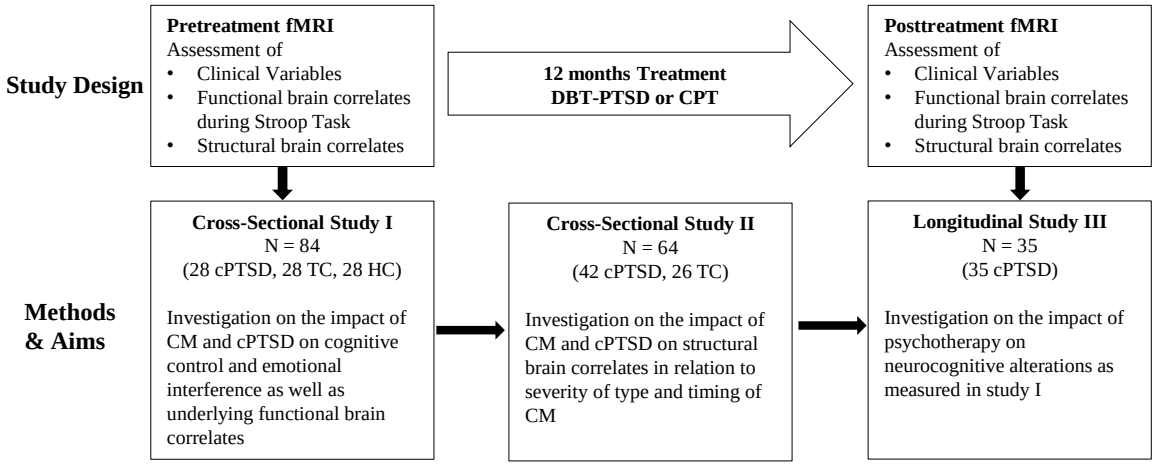

Figure 1.1 Research structure and the relationship between experimental studies

2 STUDY I: INCREASED RECRUITMENT OF COGNITIVE CONTROL IN THE PRESENCE OF TRAUMATIC STIMULI IN COMPLEX POSTTRAUMATIC STRESS DISORDER

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2.1 Abstract

A neurocircuitry model of posttraumatic stress disorder (PTSD) suggests increased amygdala responses to emotional stimuli, coupled with hypoactivation of prefrontal regions associated with cognitive control. However, results are heterogeneous across different subsamples of PTSD as well as different paradigms. We investigated cognitive control in a classic and emotional Stroop task in 28 female patients with complex PTSD (cPTSD), 28 female trauma-exposed healthy controls (TCs) and 28 female non-trauma-exposed healthy controls (HCs) using functional neuroimaging. Afterwards, we assessed memory function in a spontaneous free recall and recognition task. Patients with cPTSD displayed significantly greater Stroop interference with trauma-related words (as reflected in slower reaction times and increased errors) compared to the other conditions and compared to the TC and HC groups. Moreover, patients with cPTSD showed increased activation in the context of trauma-related words in brain regions associated with cognitive control (dlPFC, vmPFC, dACC) compared to both control groups, and a trend for increased activation in the insula compared to the HC group. Increased recruitment of regions contributing to cognitive control in patients with cPTSD, together with a lack of amygdala response may point to efforts to overcompensate for emotional distraction caused by the trauma-related words.

2.2 Introduction

The cross-national lifetime prevalence of posttraumatic stress disorder (PTSD) is estimated to be about 3.9% (Koenen et al., 2017). However, far more individuals experience a traumatic event in their lifetimes (Koenen et al., 2017). Those who develop PTSD in the aftermath of childhood interpersonal violence not only show the hallmark symptoms of PTSD such as intrusions, avoidance, numbing and hyperarousal, but usually also a range of further symptoms

which include interpersonal problems, dissociative features and severe problems in emotion regulation (Thomaes et al., 2010). This syndrome has been described as complex PTSD (cPTSD) (Cloitre et al., 2013) or as *PTSD with associated features* (American Psychiatric Association, 2013). PTSD represents an important mental disorder per se and also a frequent co-morbid disorder in a variety of clinical targets (Carletto et al., 2016; Tong et al., 2017). It has been suggested that one factor leading to the maintenance and exacerbation of PTSD symptoms (e.g., hypervigilance, intrusive thoughts, and flashbacks) may be the increased attention to threatening stimuli (Constans, 2005; Elzinga & Bremner, 2002). Likewise, impaired response inhibition of threat stimuli might reflect impaired cognitive control (i.e., inhibition of distracting stimuli). Widely used methods to study cognitive control are the classic Stroop task (CST; Stroop, 1935) and the emotional Stroop task (EST; Mathews & MacLeod, 1985). The subject has to name the color of a word as quickly as possible, ignoring the semantic content of the words. Usually, reaction times are increased for incongruent words (e.g., *BLUE* written in red) and emotionally charged words (e.g., *ATTACK*), especially when emotional words are related to the patient's psychopathology.

Several hypotheses have been developed for the classic and emotional Stroop effect. While the CST examines the general interference between conflicting processes (the tendency to say the name rather than the color), the EST assesses an attentional bias (increased selective attention) of the processing of individual-relevant information or an inability to inhibit individual-relevant information (Williams et al., 1996). Studies have repeatedly found that patients with PTSD exhibit impaired performance in both the CST (Flaks et al., 2014) and EST compared to trauma-exposed healthy controls (TCs; Khanna et al., 2015; McNally et al., 1990) and non-trauma-exposed healthy controls (HCs; Thomaes et al., 2012; Wingenfeld et al., 2011). These results suggest generally impaired inhibitory functions as well as an attentional bias to negative-valenced and especially trauma-related words compared to neutral words in patients with PTSD. However, others did not find impairments compared to TC (Cisler et al., 2011) and HC groups (Kimble et al., 2009). Related to the assumption of increased attention to threatening stimuli in patients with PTSD, multiple studies examined memory processes. Evidence was found for a memory advantage in PTSD vs. controls for negative threat information (Vrana et al., 1995) as well as an attentional bias for trauma-related material (McNally et al., 1990). Others did not find any differences in memory functions between patients with PTSD and controls (e.g., Stein et al., 1999). A variety of functional neuroimaging studies (fMRI) using Stroop-type paradigms have been used to examine brain correlates of cognitive control in PTSD (e.g., accidents or combat) and have shown increased amygdala responses to emotional

words (e.g., White et al., 2015) and disrupted recruitment of prefrontal regions associated with cognitive control, especially in the presence of emotional distracters (Blair et al., 2013; New et al., 2009). These results led to the formulation of a neurocircuitry model of PTSD (for review see, Pagani & Cavallo, 2014). This model suggests hypoactivation of prefrontal regions associated with cognitive control (dorsolateral prefrontal cortex [dlPFC], ventromedial prefrontal cortex [vmPFC, including rostral anterior cingulate cortex [rACC]]) which results in an inability to regulate affective areas (amygdala), leading to exaggerated fear response (e.g., Hughes & Shin, 2011; Rauch et al., 2006). Although this model did not originally include the dorsal ACC (dACC) and the insula, emerging evidence suggests that these regions may be hyperresponsive in PTSD and may also play an important role in this disorder (Lanius et al., 2015; Neumeister et al., 2016; Sheynin & Liberzon, 2017). However, only two studies have investigated Stroop-tasks in childhood abuse-related patients with PTSD (Bremner et al., 2004; Thomaes et al., 2012), reporting conflicting findings. In the EST, Bremner et al. (2004) observed increased dACC activation with decreased rACC and posterior insula activation in patients with PTSD compared to the TC group. Thomaes et al. (2012) who used a hybrid version of the CST and EST in cPTSD patients, found no significant group differences between patients with cPTSD and the HC group in the EST. In the CST, patients showed a trend for increased left anterior insula and dACC activation compared with the HC group (Thomaes et al., 2012). It is possible that differences in comparison groups (TC vs. HC) account for these divergent findings. One limitation of the previous fMRI studies is the absence of both matched HC and TC groups. The inclusion of both control groups provides us with the opportunity to explore whether neural abnormalities are associated with PTSD symptoms or result from the experience of the trauma alone.

Based on previous findings, the present study was designed to examine differences in brain activity in patients with childhood-abuse-related cPTSD, TC and HC groups using a hybrid version of the CST and EST (CEST) (see also, Thomaes et al., 2012). We hypothesized that compared to the TC and HC groups, patients with cPTSD exhibit increased interference for trauma-related words as reflected in overall slower reaction times and more errors in the CEST as well as in the memory tasks. We also expected increased neural activity during emotional (especially trauma-related) words in the amygdala, insula and dACC, as well as decreased activation in the dlPFC and vmPFC.

2.3 Methods

2.3.1 Participants

The sample consisted of 28 women with cPTSD and 28 female TCs, with both groups having experienced childhood sexual or physical abuse and 28 female HCs, matched for age and education. Clinical diagnoses and childhood abuse in patients with cPTSD and the TC group were assessed retrospectively by trained diagnosticians using the Structure Clinical Interview for DSM-IV Axis I Disorders (SCID-I; Wittchen et al., 1997), the Clinician Administered PTSD Scale (CAPS; Weathers et al., 2013), and the borderline personality disorder (BPD) section of the International Personality Disorder Examination (IPDE; Loranger et al., 1997). Patients with cPTSD had to fulfill the DSM-5 criteria for PTSD after sexual or physical abuse before the age of 18. Because patients with cPTSD who participated in the current study were recruited from a larger randomized controlled trial (RCT), comparing two different outpatient psychological treatments for cPTSD and co-occurring BPD-features, enrolment was restricted to women aged 18-65 who additionally had to fulfill at least three criteria of BPD (including the criterion affective instability) as defined by the IPDE, as we aimed to include highly impaired patients with cPTSD. TC and HC groups were recruited via advertisements in local newspapers, internet, and flyers. Inclusion criteria for the TC group were sexual or physical abuse before the age of 18. Exclusion criteria for the TC and HC groups were any current or previous mental disorder, any psychotherapeutic experience or any intake of psychotropic medication (for more detailed descriptions of the TC sample see: Rausch et al., 2016). General exclusion criteria were traumatic brain injuries, current and lifetime schizophrenia or bipolar-I disorder, mental retardation, severe psychopathology or somatic illness that needs to be treated immediately in another setting (e.g., BMI<16), medical conditions making exposure-based treatment impossible, a suicide attempt within the last two months, and substance dependency with no abstinence within two months prior to the study. For the current fMRI study, further exclusion criteria were metal implants, pregnancy, left-handedness, and claustrophobia. Self-report measures included retrospective questionnaires on childhood trauma (Childhood Trauma Questionnaire; CTQ; Bernstein & Fink, 1998), PTSD symptomatology (Davidson Trauma Scale; DTS; Davidson et al., 1997), and the severity of depressive mood (Beck Depression Inventory; BDI-II; Hautzinger et al., 2003). The study was approved by the Ethical Board II of Heidelberg University, Germany, and was conducted according to the Declaration of Helsinki at the Central Institute of Mental Health in Mannheim. Written informed consent was obtained

from the participants after the procedures had been fully explained. All subjects received monetary remuneration for participation in the study.

As expected, patients with cPTSD scored higher than the TC and HC groups in all clinical variables (CTQ, DTS, and BDI-II). Details on demographic data and clinical characteristics of the sample are reported in Table 2.1

Table 2.1 Demographic and clinical data in patients with complex posttraumatic stress disorder, trauma-exposed healthy subjects and non-trauma exposed healthy subjects

	cPTSD (n=28)		TC (n=28)		HC (n=28)		Statistics		Post-hoc *t* tests
	M	(SD)	M	(SD)	M	(SD)	*F*	*p*	
Demographic Data									
Age in years	30.61	(9.99)	30.21	(12.11)	30.50	(7.98)	.011	.99	
Education	n	(%)	n	(%)	n	(%)			
9 years	1	(3.57)	0	(0)	1	(3.57)	.50	.61	
10 years	11	(39.29)	9	(32.14)	8	(28.57)			
12 years	16	(57.14)	19	(67.86)	19	(67.86)			
Clinical Data									
CTQ total score	75.88	(20.10)	51.21	(13.09)	31.18	(6.76)	67.65	.001	HC<TC< cPTSD
CTQ physical abuse	11.5	(5.41)	9.36	(4.0)	5.64	(1.81)	15.23	.001	HC<TC n.s. cPTSD
CTQ sexual abuse	15.0	(6.68)	10.63	(5.59)	5.07	(0.23)	27.42	.001	HC<TC< cPTSD
DTS frequency	38.03	(10.99)	7.37	(7.30)	-	-	147.74	.001	TC< cPTSD
DTS severity	41.89	(11.86)	6.78	(9.24)	-	-	148.33	.001	TC< cPTSD
BDI- II– total score	35.39	(11.12)	3.30	(4.12)	3.39	(3.87)	184.86	.001	HC n.s. TC < cPTSD
Comorbidities	n	(%)							
BPD	17	(60.70)							
Major Depression	16	(57.10)							
Social phobia	9	(32.10)							
Specific phobia	5	(17.90)							
Panic d.	5	(17.90)							
Obsessive compulsive d.	5	(17.90)							
Bulimia n.	4	(14.30)							
Binge eating d.	3	(10.70)							
Generalized anxiety d.	2	(7.10)							
Somatization d.	1	(3.60)							
Medication	n	(%)							
Unmedicated	9	(32)							
SSRI/SNRI	13	(46)							
Other antidepressants	6	(21)							
Neuroleptics	8	(28)							
Anticonvulsants	3	(11)							

Note. cPTSD = complex post-traumatic stress disorder; TC = trauma-exposed healthy subjects; HC = non-trauma exposed healthy subjects; BPD = Borderline Personality Disorder; d. = disorder; CTQ = Childhood Trauma Questionnaire; DTS = Davidson Trauma Scale, BDI-II = Beck Depression Inventory II. M = mean; SD = standard deviation; Post-hoc *t* tests were performed at a significance level of $p<.05$ Bonferroni-corrected ; n.s.= not significant at a significance level of $p < .05$

2.3.2 Classic and Emotional Stroop Tasks

The CEST consisted of 80 randomized blocks of four words each (total 320 words), differing in word category and presented in a block-design: 20 trauma-related words (e.g., *ABUSE*), 20 general negative words (e.g., *CRY*), 20 neutral words (e.g., *SHAPE*), and four color words in congruent (e.g., *RED* written in red) as well as incongruent conditions (e.g., *RED* written in blue). Neutral words were used as baseline condition (control task). The words used in the EST were derived from a pilot study conducted with seven researchers with expertise in PTSD from our group as well as seven patients with childhood abuse-related complex PTSD (for further details see 2.6.1). Each color was assigned to a button, which participants were able to press with their right index, middle, ring, or little finger. Each word was presented four times (once in each of the four colors) for 1500 ms. Participants were asked to press the button that corresponds to the color in which the word is printed within this period. Inter-trial intervals between two words were jittered, with a mean of 300 ms. For timing efficiency, baseline-intervals (i.e., a fixation cross) between two task blocks were optimized with optseq2 (http://surfer.nmr.mgh.harvard.edu/optseq), with a mean of 798.77 ms. Before the task began, color naming was trained in 20 trials with non-word stimuli (e.g., *XXX* written in red). Immediately after the CEST, participants were asked to report all the words they remembered from the CEST in a spontaneous free recall task. Subsequently, the 60 previous words of the EST and 60 new words comparable in valence, arousal, word length, and frequency were presented randomly for an old/new-recognition task. After scanning, participants rated all words of the EST regarding valence and arousal on a five point Likert scale by the self-assessment manikin scale (SAM; Bradley & Lang, 1994) (see 2.6.2 for ratings).

2.3.3 MRI Scan Protocol

Scanning was conducted on a Siemens 3 Tesla TRIO-Scanner (Siemens Medical Solutions, Erlangen, Germany). Using three-dimensional magnetization-prepared rapid-acquisition gradient echo (MPRAGE; T1-weighted contrast, voxel size 1x1x1 mm^3), a high-resolution anatomical scan was acquired for each participant as an individual template for the functional data. The blood oxygen level-dependent signal was measured with 36 transversal slices (3 mm, descending) covering the entire brain using gradient-echo, echo-planar imaging [EPI, T2-weighted contrast, field of view=192x192 mm, voxel size 3x3x3 mm^3, 64x64 voxel matrix, flip angle 80°, echo time (TE)=30 ms, repetition time (TR)=2000 ms]. The first five scans were

discarded to minimize T1 effects. Head movement artefacts and scanning noise were restricted using head cushions and headphones.

2.3.4 Statistical Analyses

2.3.4.1 Behavioral Data

Reaction times (RTs; in ms) were log-transformed (base10) due to non-normality to minimize the effect of outliers (for review see, Ratcliff, 1993). All statistical analyses were conducted for correctly answered trials only (M=97% of all trials, SD=5.17%). Task performance (accuracy and RTs) for the CEST as well as memory function (free recall and recognition task) was analyzed via repeated measure analysis of variance (rm-ANOVAs), including the within-subject factor 'condition' (negative minus neutral, trauma minus neutral and color minus neutral; for the free recall and recognition task: negative minus neutral and trauma minus neutral) and the between-subject factor 'group' (cPTSD, TC, or HC). Post-hoc data analyses were run in order to control for the influence of early childhood traumatization and years of education on main findings. In case of significant effects for the dependent variables, post-hoc Bonferroni-corrected *t*-tests and effect sizes (partial eta-squared [η^2_p], Cohen's *d (Cohen, 1988)*) were computed. All behavioral analyses were performed with IBM SPSS Statistics 23 (IBM, USA), assuming a statistical significance level of $p<.05$, using Greenhouse-Geisser correction when necessary.

2.3.4.2 FMRI Data

Functional imaging data were analyzed using standard procedures implemented in Statistical Parametric Mapping (SPM8; http://www.fil.ion.ucl.ac.uk/spm/). The EPI time series were pre-processed according to usual practice: slice time correction, spatial realignment to the mean image to correct for head motion, co-registration onto participants' segmented high-resolution T1 scan, normalization to the standard brain of the Montreal Neurological Institute (MNI) space, and smoothing with a Gaussian kernel with full-width at half maximum of 6 mm. We did not have to exclude subjects due to excessive head motion. To control for potential artefacts, scan-to-scan movements and changes in global signal intensity were screened using the ART software package (www.nitrc.org/projects/artifact_detect). Movement was specified based on the six parameters received from the realignment step. Movements greater than 2 mm and global signal intensity changes of $z > 9$ were classified as outliers. Nuisance regressors controlling for outlier scans were introduced with the six movement regressors included as

nuisance variables in the first-level models. First-level analyses were set up according to the respective experimental conditions (with negative, trauma, color, and neutral word blocks as regressors of interest), and button presses as well as movement parameters as regressors of no interest. We defined the following contrasts at the subject level: i) negative>neutral, ii) trauma>neutral, and iii) color>neutral.

Whole-brain Voxel-wise Analysis

Data analyses at group level involved both a whole-brain voxel-wise analysis and region-of-interest (ROI) analyses to evaluate group differences during different conditions. A full factorial model (three groups x three conditions) was used including the *F* contrast 'main effect of group' (cPTSD, TC, and HC), 'main effect of condition' (negative>neutral, trauma>neutral, and color>neutral) and 'interaction effect group x condition'. A statistical threshold of $p<.05$, family-wise error (FWE) corrected was applied.

Region of interest Analysis

In line with the neurocircuitry model of PTSD and our hypotheses, we specifically hypothesized effects of emotional stimuli on limbic (amygdala, insula) and prefrontal (dlPFC, vmPFC, dACC) brain regions. Accordingly, we used anatomical masks (left and right hemisphere separately) as defined by the Automated Anatomical Labeling software (Tzourio-Mazoyer et al., 2002), smoothed with a cube of voxels of size (FWHM) 9 mm. Since our aim was to investigate posterior and anterior parts of the insula separately, anatomical masks of the insula provided by the Harvard-Oxford cortical and subcortical structural atlases (Desikan et al., 2006) were split at y=0 in anterior and posterior parts. All analyses were conducted with a threshold of $p_{(FWE)}<.05$. In case of significant differences, two-tailed post-hoc Bonferroni-corrected *t*-tests ($p<.05$) were performed using SPSS after extracting beta values of the respective peak voxel, and effect sizes (η^2_p) were computed. To check for confounding effects of CTQ score, differences in RTs as well as correct reactions on brain activation, we correlated beta values of the peak voxels with CTQ score, differences in RTs and correct reactions.

2.4 Results

2.4.1 Behavioral Results

2.4.1.1 Classic and Emotional Stroop Task Performance

Descriptive statistics for behavioral CEST performance are summarized in Table 2.2 For interference scores regarding RTs, we found a significant main effect for condition ($F_{1.81,146.57}$=28.60, p<.001, η^2_p=0.26), a significant interaction between group and condition ($F_{3.62,146.57}$=6.42, p<.001, η^2_p=0.14) as well as a trend for a group effect ($F_{2,81}$=2.69, p=.07, η^2_p=0.06). Post-hoc *t*-tests revealed significant differences between cPTSD and TC/HC groups in the trauma condition (cPTSD vs. TC: $t_{44.14}$=2.45, p<.05, d=0.68; cPTSD vs. HC: $t_{34.38}$=4.06, p<.001, d=1.19) (Figure 2.1 a). There were no significant group differences between the TC and HC groups in any condition. Regarding accuracy scores, we found a significant main effect of group ($F_{2,81}$=4.63, p<.05, η^2_p=0.10), condition ($F_{2,162}$=3.54, p<.05, η^2_p=0.04) as well as a significant interaction of group and condition ($F_{4,162}$=2.97, p<.05, η^2_p=0.07) (Figure 2.1 b). Post-hoc *t*-tests revealed significant differences between cPTSD and TC/HC groups in the trauma condition (cPTSD vs. TC: $t_{27.93}$=-2.21, p<.05, d=-0.75; cPTSD vs. HC: $t_{27.93}$=-2.15, p<.05, d=-0.72). Moreover, post-hoc *t*-tests revealed a statistical trend between cPTSD patients and the TC group in the color condition (cPTSD vs. TC: $t_{28.63}$=-1.89, p=.07, d=-0.62). There were no significant differences between the TC and HC groups in any condition (see 2.6.3 and 2.6.4 for detailed analyses). Stroop interference regarding RT and accuracy did not correlate with CTQ score. When controlling for years of education, interaction effects and main effects remained significant.

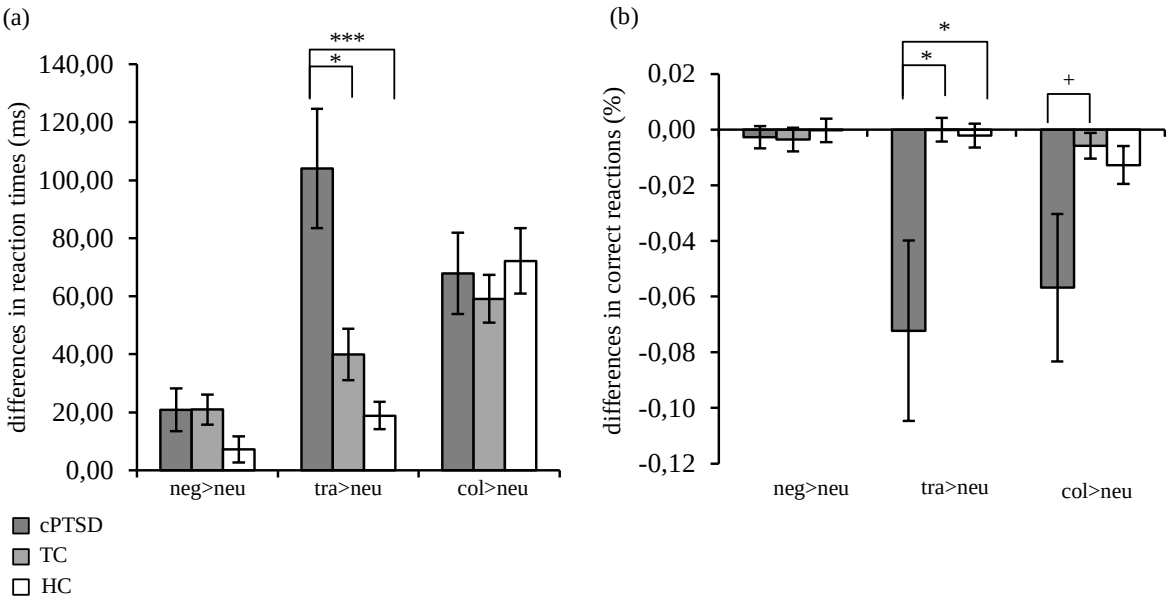

Figure 2.1 Means ± standard error of the mean (*S.E.M.*) of differences of reaction times (ms) (Figure 2.1 a) and of differences of correct reactions (%) (Figure 2.1b) in patients with complex post-traumatic stress disorder (cPTSD), trauma-exposed healthy subjects (TC) and non-trauma exposed healthy subjects (HC). Lines and asterisks above bars on bar graph indicate significant differences of post-hoc *t*-tests amongst groups during the experimental conditions. Neg>neu: negativ words minus neutral words, tra>neu: trauma-related words minus neutral words, col>neu: color words minus neutral words. *** p<.001, ** p<.01, * p<.05, +p<.09

2.4.1.2 Free Recall and Recognition Tasks

We observed a significant main effect for condition in the recall ($F_{1,81}$=177.29, p < .001, η^2_p = 0.69) as well as in the recognition task ($F_{1,81}$=99.86, p<.001, η^2_p=0.55), but no significant group difference or interaction effect between condition and group. Trauma-related words were remembered and recognized better across all groups. CTQ score and years of education did not correlate with memory functions in both tasks.

Table 2.2 Behavioral data of the classic and emotional Stroop task and related memory tasks in patients with complex post-traumatic stress disorder, trauma-exposed healthy subjects and non-trauma exposed healthy subjects, absolute values per word category

	cPTSD (n=28)		TC (n=28)		HC (n=28)	
Stroop Task						
Reaction times (ms)	M	(SD)	M	(SD)	M	(SD)
Negative words	771.56	(161.32)	661.73	(92.83)	652.42	(94.97)
Trauma-related words	854.74	(229.50)	680.75	(96.99)	664.09	(97.94)
Neutral words	750.69	(151.60)	640.79	(81.61)	645.21	(99.31)
Color words	818.58	(188.20)	699.93	(88.46)	714.42	(128.19)
Accuracy (% correct)	M	(SD)	M	(SD)	M	(SD)
Negative words	97.56	(2.93)	98.36	(2.63)	98.32	(1.96)
Trauma-related words	90.60	(17.67)	98.72	(1.81)	98.14	(2.79)
Neutral words	97.84	(2.34)	98.72	(1.53)	98.35	(2.41)
Color words	92.16	(14.99)	98.14	(2.34)	97.08	(4.41)

Table 2.2. (continued)

	cPTSD (n=28)		TC (n=28)		HC (n=28)	
Free recall (n)	M	(SD)	M	(SD)	M	(SD)
Negative words	1.54	(2.34)	1.64	(1.57)	1.61	(1.71)
Trauma-related words	5.00	(2.51)	4.71	(2.03)	4.25	(2.68)
Neutral words	0.75	(1.04)	1.29	(1.44)	1.39	(1.81)
Recognition task						
Accuracy (%correct)						
Negative words	30.75	(4.48)	30.07	(2.84)	28.93	(3.69)
Trauma-related words	34.21	(3.04)	34.36	(2.61)	32.61	(3.18)
Neutral words	29.82	(5.73)	29.96	(3.42)	28.89	(4.40)

Note. cPTSD = complex post-traumatic stress disorder; TC = trauma-exposed healthy subjects; HC = non-trauma exposed healthy subjects; M = mean; SD = standard deviation; reaction times were log-transformed for analyses and refer to correct responses.

2.4.2 FMRI Results

2.4.2.1 Whole-brain Voxel-wise Analysis

In all groups, the CEST activated similar brain areas as in prior Stroop tasks, that is, dlPFC, right amygdala, orbitofrontal cortex, superior temporal gyrus, inferior parietal lobe and occipitotemporal regions (for complete description of suprathreshold clusters of the main effect condition see chapter 2.6.5). At the whole brain level, we did not observe any clusters that survived FWE-correction for the *F* contrast group and the interaction group x condition.

2.4.2.2 Region of Interest Analysis

The ROI analyses revealed a significant interaction (group x condition) for the right dlPFC, left vmPFC, right dACC and a trend for the left dACC and right anterior insula, but not in posterior insula and amygdala (see Table 2.3 for further details and Figure 2.2 for significant clusters). In case of significant interaction effects, post-hoc Bonferroni-corrected *t*-tests between groups were calculated for each condition (see below). Brain activation did not correlate with CTQ score, differences in RTs or correct reactions.

Table 2.3 Statistic results of region of interest analyses, two-way interaction effect (group x condition)

	Location			Statistics			Coordinates (MNI)		
BA	Hemisphere R/L	Anatomical lable	Cluster	Z	*p*FWE (SVC)	η^2_p	x	y	z
9	R	Superior Frontal Gyrus	166	3.94	.01*	0.15	36	47	31
9	L	Superior Frontal Gyrus	61	3.16	.22	0.13	-39	29	37

Table 2.3 (continued)

BA	Hemisphere R/L	Anatomical lable	Cluster	Z	*p*FWE (SVC)	η^2_p	x	y	z
10	R	Middle Frontal Gyrus	70	2.83	.21	0.10	39	56	-2
10	L	Middle Frontal Gyrus	44	4.40	<.001***	0.16	-36	59	-2
32	R	Cingulate Gyrus	89	3.37	.01*	0.14	6	23	40
32	L	Cingulate Gyrus	106	3.36	.05^{+}	0.12	-3	20	37
13	R	Anterior Insula	284	3.36	.08^{+}	0.12	45	11	1
13	L	Anterior Insula	185	2.42	.62	0.08	-45	17	1
13	R	Posterior Insula	24	3.03	.18	0.10	27	17	-11
13	L	Posterior Insula	1	1.45	.94	0.06	-39	-10	19
*	R	Amygdala	8	2.00	.37	0.06	18	2	-20
*	L	Amygdala	6	2.36	.22	0.07	-30	2	-17

Note. FWE = family-wise error corrected, *p*(FWE)<.05, k>10 voxel; BA = Brodmann Area; ***p<.001, **p<.01, *p<.05, ^{+}p<.09.

DlPFC: Means and standard error of the mean of percentage signal change in the right dlPFC are displayed in Figure 2.2 a. Post-hoc *t*-tests revealed significantly higher activation during the presentation of trauma-related words in cPTSD patients compared to the TC (t_{54}=2.48, p<.05, d=0.67) and HC (t_{54}=3.17, p<.001, d=0.85) groups.

VmPFC: Means and standard error of the mean of percentage signal change in the left vmpfc are depicted in Figure 2.2 b. Post-hoc *t*-tests revealed significantly higher activation during the presentation of trauma-related words in cPTSD patients compared to the TC (t_{54}=2.53, p<.05, d=0.68) and HC ($t_{41.30}$=3.93, p<.001, d=1.10) groups.

DACC: Means and standard error of the mean of percentage signal change in the right and left dACC are depicted in Figure 2.2 c and 2.2 d. Post-hoc *t*-tests revealed significantly higher activation during the presentation of trauma-related words in cPTSD patients compared to the TC (right dACC: t_{54}=2.27, p<.05, d=0.61; left dACC: $t_{43.53}$=2.73, p<.05, d=0.75) and HC (right dACC: $t_{40.72}$=3.30, p<.001, d=0.92; left dACC: $t_{40.99}$=3.41, p<.001, d=0.95) groups.

Insula: Means and standard error of the mean of percentage signal change in the right anterior insula are displayed in Figure 2.2 e. Post-hoc *t*-tests showed significantly higher activation during the presentation of trauma-related words in cPTSD patients compared to the HC group (t_{54}=4.54, p<.001, d=1.23). Post-hoc comparisons between TC and cPTSD or rather TC and HC groups revealed no significant differences.

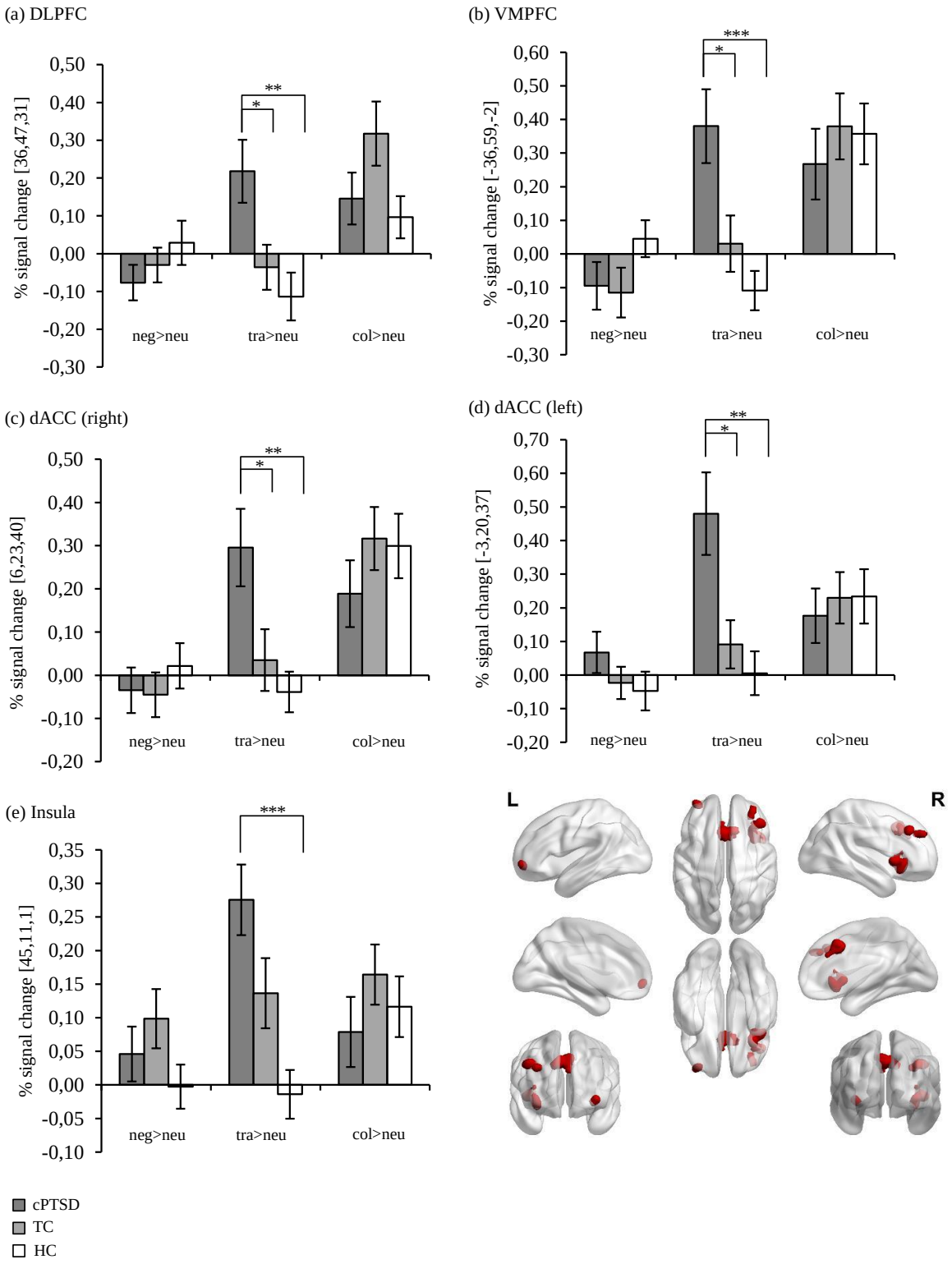

Figure 2.2 Results of the region of interest (ROI) analyses: Significant clusters in the two-way interaction effect (group x condition) and percentage signal change during the experimental conditions (neg>neu, tra>neu, col>neu) for (a) the dorsolateral prefrontal cortex (DLPFC; [36,47,31]), (b) ventromedial prefrontal cortex (VMPFC; [-36,59,-2]), (c) right dorsal anterior cingulate cortex (dACC; [6,23,40]), (d) left dorsal anterior cingulate cortex (dACC; [-3,20,37]) and (e) insula [45,11,1] in patients with complex post-traumatic stress disorder (cPTSD), trauma-exposed healthy subjects (TC) and non-trauma exposed healthy subjects (HC). Error bars represent standard error of the mean (*S.E.M.*). Lines and asterisks above bars on bar graph indicate significant differences of post-hoc *t*-tests amongst groups during the experimental conditions. Neg>neu: negativ words minus neutral words, tra>neu: trauma-related words minus neutral words, col>neu: color words minus neutral words. ***p<.001, **p<.01,*p<.05

2.5 Discussion

The goal of the present study was to examine changes in brain activity in patients with childhood abuse-related cPTSD and TC and HC groups. Increased stroop interference in cPTSD patients, as marked by slower RTs and more errors, was significantly increased for trauma-related words compared to both control groups. Thus, the present data suggest a specific attentional bias and greater interference in patients with cPTSD towards trauma-related stimuli. This has been shown repeatedly in patients with PTSD (e.g., Williams et al., 1996) which is in line with the symptoms of hyperarousal, intrusions, and enhanced attention to threatening stimuli. Moreover, in the context of trauma-related words, patients with cPTSD showed increased activation in the dlPFC, vmPFC and dACC compared to both control groups and a trend for increased activation in the right anterior insula compared to the HC group.

In line with our hypotheses, patients with cPTSD showed increased dACC activation during trauma-related stimuli compared to both control groups. The literature contains supporting data regarding activation of dACC in PTSD patients, with higher dACC activation found using CST (Thomaes et al., 2012), EST (Bremner et al., 2004), counting Stroop (Shin et al., 2007) and affective Stroop (White et al., 2015). The dACC has been shown to be reliably activated in interference paradigms such as the Stroop task (Xu et al., 2016). Higher dACC activation in our cPTSD sample may reflect greater response conflicts and might increase cognitive resources in the trauma condition vs. other conditions (Shin et al., 2007). The dACC is also discussed to be part of the salience network, which may play a role in hypervigilance in PTSD. Therefore, higher dACC activation might reflect a state of high arousal and attention in cPTSD that is specifically caused by trauma-related information (Hayes et al., 2012a). Bush et al. (1998) demonstrated that significant activation in dACC was related to response time increases across conditions. Yet in our study, activation of this region was not accompanied by significant response time increases in cPTSD patients.

As expected, patients with cPTSD revealed a trend for increased activation in the anterior insula compared to the HC group when presented with trauma-related words. These results are in line with several previous studies, suggesting increased activation in the insula in PTSD patients when presented with trauma (Lanius et al., 2007), negative (Bruce et al., 2012) and non-emotional cues (Thomaes et al., 2012). However, another study using the EST found decreased posterior insula activation (Bremner et al., 2004).

Several studies have shed light on differences between functional circuits associated with the anterior and posterior insula. As extensively reviewed, the anterior and posterior insular cortices

have different patterns of connectivity with other brain regions (Menon & Uddin, 2010). Results suggest an important role for the anterior insula with regard to cognitive control, salience detection and attentional processes (Nelson et al., 2010). It is discussed as an integral hub mediating information flow across brain networks involved in attentional processing and cognition, whereas more sensory attributes and interoception are thought to be represented in posterior insula (Craig, 2010; Menon & Uddin, 2010). In this case, hyperactivity of the anterior insula might be related to pathologically enhanced salience detection (Menon & Uddin, 2010). Moreover, previous work provides evidence that the right anterior insula is among others involved in response inhibition of a prepotent behavior in case of response-conflict tasks (Sharp et al., 2010). Therefore, our finding of increased anterior insula activation may point either to higher arousal in patients with cPTSD in response to trauma-related stimuli, or to a greater response-conflict in case of trauma-related stimuli. The latter would be in line with activation of the anterior insula in all groups during the color condition. Possibly, our study design was suited to elicit effects in the anterior insula, but not in the posterior insula. Future studies might further investigate this issue of differences between functional circuits of the anterior and posterior parts of the insula in cPTSD. The TC group did not differ significantly from patients with cPTSD or from the HC group. This is not in line with Lindauer et al. (2008) demonstrating greater insula activation during script-driven imagery in PTSD patients compared to a TC group. One may explain this divergent finding with sample characteristics (cPTSD vs. single-trauma) or different paradigms (stroop vs. script-driven imagery).

Contrary to our hypothesis, we did not find higher amygdala activity in response to trauma-related words compared to neutral words in patients with cPTSD as observed in previous studies (Blair et al., 2013; Dannlowski et al., 2012; White et al., 2015). Some recent studies have also failed to find alterations in amygdala activity in PTSD patients in response to trauma-related cues (Fani et al., 2012; Fonzo et al., 2016; Thomaes et al., 2012). One possibility relates to the contextual demands of the CEST which may not have been optimally suited to elicit effects in the amygdala, but rather engaged prefrontal regions that subserve functions of cognitive control (dlPFC, vmPFC, dACC). Moreover, previous meta-analyses of functional neuroimaging studies on emotion processing in depression (Delaveau et al., 2011) and BPD (Schulze et al., 2016) showed dampening effects of medication on amygdala activity. Several studies have also reported attenuated amygdala activation corresponding with increased dlPFC activity (Fonzo et al., 2016; Mitchell et al., 2007). These results are supported by a meta-analysis, showing attenuated amygdala activity in the context of increasing attentional demands (Costafreda et al., 2008).

Our findings differ from previous fMRI studies that have typically found decreased activation in the dorsal, lateral and ventral PFC regions (Hayes et al., 2012a; Hughes & Shin, 2011). The current results point to greater dlPFC and vmPFC engagement in cPTSD patients during trauma-related words compared to both control groups. However, more recent studies have been consistent with our results with greater dlPFC (Fonzo et al., 2016; White et al., 2015) and vmPFC (Bruce et al., 2012; Bryant et al., 2008) activation. Fonzo et al. (2016) found greater dlPFC activation in response to negative stimuli in PTSD patients after childhood maltreatment compared to PTSD patients with no childhood maltreatment history. In a sample of sub-threshold military patients with PTSD symptoms, White et al. (2015) showed increased interference and increased activation in the dorsal lateral regions in response to emotional (relative to neutral) stimuli in participants with greater symptom severity. We suggest that increased dlPFC response in our cPTSD sample relates to task demands specific for CEST. It is most likely that trauma-related words in the context of this cognitive paradigm were distressing to patients with cPTSD. The aim of responding as quickly as possible to the correct color while being confronted with trauma-related words may have activated cognitive control networks. Therefore, increased dlPFC activation might reflect higher expenses of cognitive control resources to trauma-related cues in cPTSD patients compared to TC and HC groups, or may be a compensatory mechanism to correct for enhanced attentional threat orientation to task-relevant demands (Comte et al., 2016).

Contrary to our hypothesis, we found greater vmPFC activation in cPTSD patients during trauma-related words compared to both control groups. However, as many studies also found hyperactivation in vmPFC regions, this result is convergent with some previous studies. In a sample of Iraq war veterans, Morey et al. (2008) showed hyperactivity in the vmPFC in PTSD patients during processing of trauma-related vs. trauma-unrelated material. Further studies demonstrated hyperactivation within vmPFC regions in PTSD patients during an auditory oddball paradigm (Bryant et al., 2005), response-inhibition task (Carrion et al., 2008) and script driven imagery of childhood trauma (Shin et al., 1999). It is important to note that the vmPFC subserves different functions of both inhibition (successful suppression of emotional responses to a negative emotional signal) or rather emotion regulation and facilitation of autonomic arousal (Hayes et al., 2012a; Quirk & Beer, 2006). Thus, our findings may reflect increased effort in the trauma vs. other conditions in the cPTSD group as well as regulation of autonomic arousal during the cognitive task.

In order to differentiate between the long-lasting effects of childhood abuse and consequences of cPTSD, we included a TC control group. On the behavioral level as well as on the neural

level (except for the anterior insula), the TC group revealed significant differences to the cPTSD group, but no significant differences compared to the HC group in any condition. These results are in line with Cisler et al. (2011) who also did not find any attention bias towards trauma-related words in the TC group. The current fMRI data are not in line with another study, showing superior recruitment of regions implicated in cognitive control in a TC group compared to patients with PTSD and a HC group (Blair et al., 2013). The current results suggest that the attentional bias to trauma-related stimuli and corresponding alterations in prefrontal brain regions are related to cPTSD and not to trauma exposure itself. One could speculate that the TC group was not distracted by the trauma-related stimuli, which in turn could be a crucial resilience factor that could prevent the development of cPTSD (Constans, 2005).

Patients with cPTSD showed neither impairments nor advantages in memory functions for threat information, as examined in the free recall and recognition tasks. This is in line with Stein et al. (Stein et al., 1999) who found no differences in patients with PTSD in an explicit memory task. The data are not in line with studies demonstrating evidence for a memory advantage in patients with PTSD vs. TC/HC groups for threat information (Paunovi et al., 2002; Vrana et al., 1995). These studies suggest that patients with cPTSD do not exhibit impaired encoding and memory for traumatic information.

While the present study had a number of strengths, including a representative cPTSD group sample after childhood abuse, a TC and HC group sample (matched regarding age and education), several limitations are worth noting. First, the inevitable use of psychotropic medication in our cPTSD sample has to be considered. While some studies did not find any influence of psychotropic medication on cognitive and psychomotor performance (Paul et al., 2007) as well as emotion processing and brain activity (van Tol et al., 2011), other studies point to significant influences on cognitive performance and emotion processing caused by differences in pharmacological profiles (Outhred et al., 2014; Schmitt et al., 2001). Therefore, we cannot rule out that medication effects might have confounded our results. To clarify the role of medication on cognitive performance and emotion processing in cPTSD, future studies would need to recruit drug-naive cPTSD patients. Second, the majority of our cPTSD sample had a high rate of comorbid BPD, major depression and social anxiety. Given that cPTSD after childhood abuse is associated with high co-occurring symptoms of depression, interpersonal problems and anxiety as well as personality disorders (Kessler et al., 1997; Zanarini et al., 1998), our sample is representative for this group of patients. However, it could be argued that these comorbid disorders (especially BPD and major depression), rather than cPTSD accounted for the observed results. Thus, future research might study cPTSD patients, BPD, major

depression, and social anxiety disorders separately to strengthen the internal validity of the psychobiology of PTSD. However, this would come at the expense of external validity, as the syndrome of cPTSD is defined by symptoms and comorbidity with the respective disorders. Moreover, we only included female patients. Consequently, the results of our study are restricted to a female sample of cPTSD patients and cannot be generalized to male patients, who might show other reactions to trauma-related cues. However, most studies on PTSD in the general population have found higher rates of PTSD in women than in men (especially after childhood interpersonal violence) (Olff et al., 2007; Tolin & Foa, 2006) and men are less likely to seek psychotherapy (Yousaf et al., 2015). Moreover, fMRI studies have also reported gender-related differences in terms of BOLD activation in prefrontal and limbic regions during emotional and cognitive tasks, and it is therefore useful to include a homogenous sample of either women or man (Lopez-Larson et al., 2011). Third, we used congruent and incongruent color words as one condition in the CST. As a consequence, we were not able to analyze the CST separately. Fourth, although groups were matched for demographic parameters and age, patients with cPTSD reported more severe traumatic experiences compared to the TC group, as measured with the CTQ. However, post-hoc analyses suggest no significant association of our results with cPTSD patients' trauma experience as measured by CTQ. Finally, it has to be noticed that our statistics are limited by low statistical power, which might have caused false negative results. With the given sample of n=84, α=.05 and β=.05, 3 between-subject factors and 3 within-subject factors, a sensitivity power analysis conducted with G*Power (Faul et al., 2007) indicated that the smallest interaction effect that can be ruled out is Cohen's f=0.34. This means that we cannot rule out medium or small effects (f=0.25 or less) (according to Cohen, 1988) with sufficient certainty, given the sample size.

Taken together, our results are not completely in line with the hypothesized neurocircuitry model of PTSD. We could replicate increased dACC and a trend for increased insula activation during trauma-related stimuli in cPTSD patients, but did not find increased amygdala activation. Moreover, we found greater dlPFC and vmPFC activation in the presence of trauma-related words. Greater activation in these brain regions, which subserve inhibition of distracting stimuli, attentional control and emotion regulation, together with no significant group differences with regard to amygdala response may reflect the cognitive demands of the stroop task and may point to efforts to compensate for emotional distraction caused by the trauma-related words in cPTSD (Eysenck et al., 2007).

2.6 Supplementary Material

2.6.1 Pilotstudy: Selecting Words for the Emotional Stroop Task

Seven experts for PTSD from the Department of Psychosomatic Medicine and Psychotherapy of the Central Institute of Mental Health in Mannheim categorized 400 words of the corpus-based wordlist (Institut für Deutsche Sprache, 2013, http://www.ids-mannheim.de/derewo) into trauma-related, generally negative, neutral and *other* word category. Out of the words categorised concordantly into the same category, 40 words were selected for each category (trauma-related, generally negative, neutral), and matched for length and frequency. In a second step, seven patients with childhood abuse-related complex PTSD from the inpatient unit rated these words regarding valence and arousal on a five point likert scale by the self-assessment manikin scale (SAM). According to the patient ratings, we selected 20 words for each category (see Figure 2.3). Table 2.4 shows the finally wordlist of the Classic and Emotional Stroop Task.

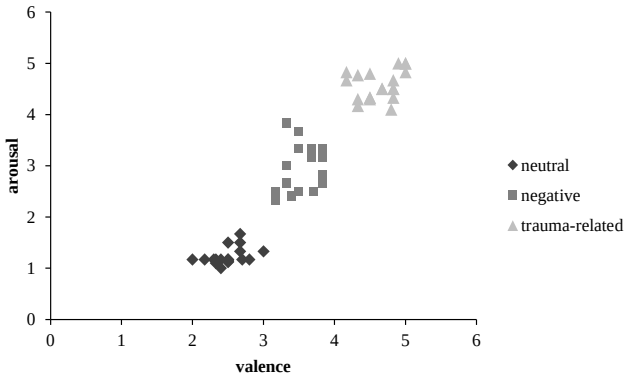

Figure 2.3 Arousal and valence ratings of the finally selected words for the Emotional Stroop Task

Table 2.4 Wordlist of the classic Stroop task, the emotional Stroop task and the Recognition task in German (English translation in italics).

Classic Stroop	Emotional Stroop			Recognition Task		
	trauma	negative	neutral	trauma	negative	neutral
Blau	ausgeliefert	Beschwerde	Anlage	Penetration	Attentat	Abendprogramm
blue	*to be at someone's mercy*	*complaint*	*investment*	*penetration*	*assassination*	*evening program*
Grün	Brust	Biest	bedeuten	Peinigung	Beanstandung	Schreibheft
green	*breast*	*beast*	*to mean something*	*torment*	*objection*	*writing book*
Rot	Busen	Entsetzt	Fisch	Quälerei	Beerdigung	Bindestrich
red	*bosom*	*horrified*	*fish*	*agony*	*funeral*	*hyphen*
Gelb	Erektion	Giftgas	formen	Drangsalieren	weinen	prägen
yellow	*erection*	*poison gas*	*form*	*harass*	*cry*	*shape*

Table 2.4 (continued)

Emotional Stroop			Recognition Task		
erregt	Giftmord	Fragezeichen	prügeln	einbüßen	beinhalten
aroused	*murder by poisoning*	*question mark*	*thrash*	*forfeit*	*contain*
Gewalt	Habgier	Käuferin	Schande	Knall	Dampfer
violence	*greed*	*buyer*	*shame*	*bang*	*steamer*
hilflos	Infekt	lesbar	Folter	Malheur	Entwurf
helpless	*infection*	*readable*	*torture*	*mishap*	*draft*
Missbrauch	Last	logisch	schutzlos	entrüstet,	händisch
abuse	*burden*	*logical*	*unprotected*	*enraged*	*manually*
Misshandlung	pleite	manuell	ohnmächtig	heimtückisch	goldfarben
mistreatment	*bankrupt*	*manual*	*unconscious*	*sneaky*	*gold-colored*
Oralsex	Schuss	Mappe	machtlos	unnötig	klar
oral sex	*shot*	*file*	*powerless*	*unnecessary*	*clear*
Penis	sinnlos	Maß	Blowjob	Giftspritze	Blumenvase
penis	*senseless*	*measure*	*blowjob*	*poison syringe*	*flower vase*
quälen	Spinne	Notizblock	Schoß	Chemiewaffe	Briefträger
agonize	*spider*	*notepad*	*lap*	*chemical weapon*	*postman*
Scheide	Sturz	Poster	Vulva	Ausbeutung	Weizen
vagina	*plunge*	*poster*	*vulva*	*exploitation*	*wheat*
schlagen	Terroranschlag	Postler	Samenerguss	Entzündung	Bild
hit	*terrorist attack*	*post office worker*	*ejaculation*	*inflammation*	*picture*
Schuld	Trauerfeier	Rahmenprogramm	Beischlaf	Kummer	Einheit
guilt	*funeral service*	*supporting program*	*sexual intercourse*	*grief*	*unity*
Sex	trauern	Roggen	Ständer	Verfall	Kundin
sex	*grieve*	*rye*	*boner*	*deterioration*	*customer*
Sperma	Unfall	Schiff	Schwanz	Monster	Ordner
sperm	*accident*	*ship*	*cock*	*monster*	*folder*
Vagina	verlieren	silberfarben	kribbelig	arm	verstehbar
vagina	*lose*	*silver-colored*	*tingly*	*poor*	*understandable*
Vergewaltigung	verräterisch	Tanne	Brustwarze	Fall	Teich
rape	*treacherous*	*fir tree*	*nipple*	*case*	*pond*
wehrlos	Verwesung	Tontopf	Büste	Insekt	Baum
defenseless	*decay*	*clay pot*	*bust*	*insect*	*tree*

2.6.2 Valence and Arousalratings

Table 2.5 Valence- and arousalratings of the words of the Emotional Stroop task in patients with complex posttraumatic stress disorder, trauma-exposed healthy subjects and non-trauma exposed healthy subjects

	Descriptives						Statistics		
	cPTSD (n=28)		TC (n=28)		HC (n=28)				
	M	(SD)	M	(SD)	M	(SD)	*F*	*p*	Post-hoc *t* tests
Valence									
Negative words	3.83	(0.34)	3.92	(0.44)	3.80	(0.54)	n.s.	n.s.	n.s.
Trauma-related words	4.46	(0.34)	3.68	(0.32)	3.51	(0.42)	46.57	<.001	cPTSD>TC ns. HC
Neutral words	2.51	(0.53)	2.63	(0.47)	2.81	(0.38)	n.s.	n.s.	n.s.
Arousal									
Negative words	2.64	(0.67)	2.28	(0.88)	1.86	(0.65)	6.24	<.05	cPTSD n.s. TC n.s HC cPTSD> HC
Trauma-related words	3.97	(0.61)	2.43	(0.68)	2.02	(0.72)	52.92	<.001	cPTSD>TC ns. HC
Neutral words	1.17	(0.18)	1.12	(0.43)	1.04	(0.12)	n.s.	n.s.	n.s.

Note. cPTSD = complex posttraumatic stress disorder; TC = trauma-exposed healthy subjects; HC = non-trauma exposed healthy subjects; M = mean; SD = standard deviation; Post-hoc *t* tests were performed at a significance level of $p<.05$ Bonferroni-corrected; n.s.= not significant at a significance level of $p<.05$

2.6.3 Overview of the Results of the Repeated Measure Analysis of Variance

Table 2.6 Overview of the results of the repeated measure analysis of variance (rm-ANOVAs) of the classic and emotional Stroop task and related memory tasks in patients with complex posttraumatic stress disorder, trauma-exposed healthy subjects and non-trauma exposed healthy subjects

	Main effect group	Main effect condition	Interaction group x condition
Stroop Task			
Reaction times (lg)	$F_{(2,81)}=2.69$, $p=.07^{+}$, $\eta^2_p= 0.06$	$F_{(1.81, 146.57)}=28.60$, $p<.001$***, $\eta^2_p=0.26$	$F_{(3.62, 146.57)}=6.42$, $p<.001$***, $\eta^2_p=0.14$
Accuracy (% correct)	$F_{(2,81)}=4.63$, $p<.05$*, $\eta^2_p= 0.10$	$F_{(2, 162)}=3.54$, $p<.05$*, $\eta^2_p=0.04$	$F_{(4, 162)}=2.97$, $p<.05$*, $\eta^2_p=0.07$
Memory Tasks			
Free recall (n)	$F_{(2,81)}=2.41$, $p=.10$, $\eta^2_p=0.06$	$F_{(1, 81)}=177.29$, $p<.001$***, $\eta^2_p=0.69$	$F_{(2, 81)}=1.07$, $p=.35$, $\eta^2_p=0.03$
Recognition task Accuracy (% correct)	$F_{(2,81)}=0.36$, $p=.70$, $\eta^2_p=0.01$	$F_{(1, 81)}=99.86$, $p<.001$***, $\eta^2_p=0.55$	$F_{(2, 81)}=0.42$, $p=.66$, $\eta^2_p=0.01$

Note. cPTSD = complex posttraumatic stress disorder; TC = trauma-exposed healthy subjects; HC = non-trauma exposed healthy subjects, Rm-ANOVAs include the within-subject factor condition (negative minus neutral, trauma minus neutral and color minus neutral; for the free recall and recognition task: negative minus neutral and trauma minus neutral) and the between-subject factor group (cPTSD, TC, or HC); Significance level $p<.05$; ***$p<.001$, **$p<.01$, *$p<.05$, $^{+}p<.09$

2.6.4 Overview of the Post-hoc *t*-tests of the Classic and Emotional Stroop Task and Related Memory Tasks

Table 2.7 Overview of the post-hoc t-tests of the classic and emotional Stroop task and related memory tasks in patients with complex posttraumatic stress disorder, trauma-exposed healthy subjects and non-trauma exposed healthy subjects

	cPTSD vs. TC	cPTSD vs. HC	TC vs. HC
Stroop Task Reaction times (lg)			
Negative>neutral	$T_{(54)}$=-0.38, p=.71, d=-0.10	$T_{(54)}$=1.33, p=.19, d=0.36	$T_{(54)}$=1.31, p=.20, d=0.35
Trauma>neutral	$T_{(44.14)}$=2.45, p<.05*, d=0.68	$T_{(34.38)}$=4.06, p<.001***, d=1.19	$T_{(54)}$=1.42, p=.16, d=0.38
Color>neutral	$T_{(54)}$=-0.39, p=.70, d=-0.10	$T_{(54)}$=-0.98, p=.33, d=-0.26	$T_{(54)}$=-0.72, p=.48, d=-0.19
Accuracy (% correct)			
Negative>neutral	$T_{(54)}$=0.15, p=.88, d=0.04	$T_{(54)}$=-0.42, p=.68, d=-0.11	$T_{(54)}$=-0.56, p=.58, d=-0.15
Trauma>neutral	$T_{(27.93)}$=-2.21, p<.05*, d=-0.75	$T_{(27.93)}$=-2.15, p<.05*, d=-0.72	$T_{(54)}$=0.36, p=.72, d=0.10
Color>neutral	$T_{(28.63)}$=-1.89, p=.07^{+}, d=-0.62	$T_{(30.55)}$=-1.61, p=.12, d=-0.50	$T_{(54)}$=0.84, p=.40, d=0.23
Memory tasks			
Free recall (n)			
Negative>neutral words	$T_{(54)}$=0.84, p=.41, d=0.22	$T_{(54)}$=1.19, p=.24, d=0.32	$T_{(54)}$=0.28, p=.78, d=0.07
Trauma>neutral words	$T_{(54)}$=1.42, p=.16, d=0.38	$T_{(54)}$=1.21, p=.22, d=0.36	$T_{(54)}$=1.07, p=.29, d=0.29
Recognition task			
Accuracy (n)			
Negative>neutral words	$T_{(54)}$=0.87, p=.39, d=0.23	$T_{(54)}$=0.89, p=.38, d=0.24	$T_{(54)}$=0.08, p=.94, d=0.02
Trauma>neutral words	$T_{(44.15)}$=0.00, p=1, d=0.00	$T_{(48.51)}$=0.55, p=.58, d= 0.15	$T_{(54)}$=0.73, p=.47, d=0.20

Note. cPTSD = complex posttraumatic stress disorder; TC = trauma-exposed healthy subjects; HC = non-trauma exposed healthy subjects, Significance level p<.05; Adjustment for multiple comparisons: Bonferroni, ***p<.001, **p<.01, *p<.05, ^{+}p<.09

2.6.5 Whole Brain Results

Table 2.8 Whole-brain results for the F contrast 'main effect of condition' (within the 3 x 3 full factorial model)

Anatomical label	BA	Cluster size	Peak voxel (MNI)			Voxel Z	*p*FWE
			x	y	z		
Lingual Gyrus	17	1689	-9	-88	1	Inf	<.0001
Inferior Parietal Lobule	40	3478	-48	-43	46	Inf	<.0001
	11	3195	-3	47	-14	Inf	<.0001
Medial Frontal Gyrus							
Middle Temporal Gyrus	21	220	-57	-4	-14	Inf	<.0001
Middle Frontal Gyrus	46	2394	-45	35	25	Inf	<.0001
Posterior Lobe	*	448	-9	-76	-26	7.836	<.0001
Posterior Lobe	*	127	24	-82	-32	7.402	<.0001

Table 2.8 (continued)

Anatomical label	BA	Cluster size	Peak voxel (MNI) x	y	z	Voxel Z	*p*FWE
Middle Temporal Gyrus	37	149	-54	-49	-8	7.335	<.0001
Posterior Lobe	*	222	36	-67	-44	7.143	<.0001
Temporal Lobe	*	98	60	-46	-5	7.105	<.0001
Superior Temporal Gyrus	38	27	45	20	-26	6.748	<.0001
Limbic Lobe	Amygdala	46	21	-7	-14	6.204	<.0001
Superior Temporal Gyrus	22	59	54	-10	-11	6.195	<.0001
Sub-lobar	Hypothalamus	53	6	-4	-2	5.718	<.0001
Inferior Temporal Gyrus	37	15	-42	-46	-17	5.318	.003

Note. FWE = family-wise error corrected, *p*(FWE) <.05, k > 10 voxel; BA = Brodmann area.

3 STUDY II: INFLUENCE OF SEVERITY OF TYPE AND TIMING OF RETROSPECTIVELY REPORTED CHILDHOOD MALTREATMENT ON FEMALE AMYGDALA AND HIPPOCAMPAL VOLUME

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3.1 Abstract

Deleterious effects of adverse childhood experiences (ACE) on human brain volume are widely reported. First evidence points to differential effects of ACE on brain volume in terms of timing of ACE. Upcoming studies additionally point towards the impact of different types (i.e., neglect and abuse) of ACE in terms of timing. The current study aimed to investigate the correlation between retrospectively reported severity of type (i.e., the extent to which subjects were exposed to abuse and/or neglect, respectively) and timing of ACE on female brain volume in a sample of prolonged traumatized subjects. A female sample with ACE (N=68) underwent structural magnetic resonance imaging and a structured interview exploring the severity of ACE from age 3 up to 17 using the *Maltreatment and Abuse Chronology of Exposure* (MACE).
Random forest regression with conditional interference trees was applied to assess the impact of ACE severity as well as the severity of ACE type, (i.e., to what extent individuals were exposed to neglect and/or abuse) at certain ages on pre-defined regions of interest such as the amygdala, hippocampus, and anterior cingulate volume. Analyses revealed differential type and timing-specific effects of ACE on stress sensitive brain structures: Amygdala and hippocampal volume were affected by ACE severity during a period covering preadolescence and early adolescence. Crucially, this effect was driven by the severity of neglect.

3.2 Introduction

Adverse childhood experiences (ACE), i.e., sexual or physical abuse or neglect during childhood, are highly prevalent worldwide (Koenen et al., 2017). Particularly prolonged and repeated ACE constitutes a major risk factor for adult psychopathology (Teicher et al., 2016) such as major depression (Gerke et al., 2018), substance abuse (Rasmussen et al., 2018), personality disorders (Battle et al., 2004), anxiety disorders, and posttraumatic stress disorder

(PTSD) (Gilbert et al., 2009). ACE is further linked to deleterious effects on neurocognitive functioning (i.e., working memory and inhibitory control), mirrored in significant functional and structural alterations in stress and emotion sensitive brain regions such as in the amygdala, hippocampus, as well as in the anterior cingulate cortex (ACC) (for reviews see, Teicher & Samson, 2016; Teicher et al., 2016). It has been hypothesized that the latter brain regions are particularly vulnerable to the impact of ACE due to a high density of glucorticoid receptors; hence prolonged release of glucocorticoids is stated to cause damage, dendritic atrophy and neurogenesis suppression (Calem et al., 2017; Teicher & Samson, 2016). Yet, although the direction in terms of a reduction or enlargement of these regions varies across studies (Teicher & Samson, 2016; Yehuda et al., 2015), volumetric changes in stress and emotion associated brain regions are hypothesized to play a pivotal role in individual differences contributing to resilience or vulnerability in the aftermath of ACE, emphasizing the need to understand modulating factors of the relationship between brain volume and ACE.

Building on evidence from animal models, a novel conceptual framework has been proposed, which is increasingly highlighted in the field - deconstructing ACE into at least two underlying dimensions: *active* and *passive* maltreatment that may distinctly impact neural development (Sheridan & McLaughlin, 2014). Active maltreatment represents harmful experiences, challenging the physical integrity of the self, e.g., physical and sexual abuse (Sheridan & McLaughlin, 2014). Passive maltreatment consists of the absence of social and cognitive environmental input, which is necessary to fulfil the basic needs of a child, i.e., emotional and physical neglect (Sheridan & McLaughlin, 2014). Animal studies allow the development of experimental protocols in which animals are exposed to acute and/or chronic stress (Lupien et al., 2009). Hence, the cause–effect relationship between stress and its impact on the brain can be directly demonstrated. Experimental stressful *early-life* manipulations in animals include e.g. separating the animal from its mother, modifying maternal behavior, or exposing the animal to synthetic glucocorticoids (Lupien et al., 2009). Animals exposed to stress pre- or postnatally show a wide range of changes in the brain's neurochemical system, exhibit more learning errors and show alterations of the sensitivity of the HPA axis, thereby potentially altering the animal's ability to regulate their emotional states (Nelson, 1999). Due to ethical issues, the cause–effect impact of stress on the brain cannot be studied in humans, and therefore human studies are correlational by nature, as the experience of abuse and neglect co-occur at extremely high rates in children and adolescents (McLaughlin et al., 2012). Consequently, finding individuals who only experienced one form of adversity would not only be difficult, but also would not accurately represent the population of children and adolescents exposed to ACE. Therefore, it

seems reasonable to use the dimensions that are the severity of ACE types (i.e., abuse and neglect severity) within one sample, instead of separate categories (i.e., abuse vs. neglect). Studies focusing on passive maltreatment in subjects are predominantly those of early deprivation in institutionally reared children. In the English and Romanian Adoptees study, significantly smaller white and gray matter volume, as well as smaller volume of the left hippocampus, and larger volume in the right amygdala was observed for institutionalized adolescents adopted from Romania to the United Kingdom vs. never-institutionalized adoptees from the United Kingdom (Mehta et al., 2009; but see Tottenham et al., 2010). Moreover, a randomized clinical trial compared children, who remained in an institution in Bucharest to those that have been placed into high-quality foster care during early childhood and to non-institutionalized children. Children exposed to institutional rearing showed decreased cortical gray matter and white matter compared to non-institutionalized children. However, children who were placed into foster care did not significantly differ in their white matter volume from those children reared in biological families (Sheridan et al., 2012). Interestingly, no effects of institutionalization were found on subcortical regions such as the hippocampus and the amygdala. Studies focusing on active maltreatment, i.e., abuse, found evidence for a negative relation between (sexual) abuse and the size of the hippocampus (Andersen et al., 2008), visual cortex, as well as somatosensory cortex (Andersen et al., 2008; Heim et al., 2013; Tomoda et al., 2012). These results have to be interpreted with caution, due to the fact that abuse is usually accompanied by neglect (Bick & Nelson, 2016), making it difficult to study the relative contribution of abuse on development.

Only two studies directly compared childhood abuse and childhood deprivation so far. Everaerd et al. (2016) found reduced volume in the fusiform gyrus and middle occipital gyrus in individuals exposed to deprivation, compared to those exposed to abuse, while volume alterations in somatosensory areas (posterior precuneus, postcentral gyrus) were further modulated by gender (Everaerd et al., 2016). Moreover, Teicher et al. (2018) showed that male hippocampal volume was associated with neglect, while female hippocampal volume was associated with abuse (Teicher et al., 2018).

The brain is shaped not only by the *type* of ACE encountered during development, but also by *timing*, referring to when ACE were experienced during brain development (Teicher & Samson, 2016). Neuronal plasticity is defined as the ability of the brain to adapt its structure and function in response to environmental demands, experiences and physiological changes (Hubener & Bonhoeffer, 2014; Pascual-Leone et al., 2005). Crucially, the human brain remains plastic throughout the whole life span (Hubener & Bonhoeffer, 2014; Lupien et al., 2009), whereby

the degree of plasticity seems to be modulated by varying maturation trajectories of different brain regions (Brydges, 2016; Lupien et al., 2009). In this light, one might has the possibility to detect the timing of the higher impact of ACE on neuroanatomical measurements. Recent investigations have therefore addressed the question, whether ACE has a distinct impact on brain morphology during specific time windows. Pechtel et al. (2014), showed that the right amygdala was affected by exposure to maltreatment at 10–11 years of age, and that only a modest degree of exposure was required to produce maximal hypertrophy (Teicher & Samson, 2016). Moreover, they found that right hippocampal volume appeared to be most affected to maltreatment at 7 and 14 years of age. A further study in women with a history of sexual abuse found evidence of a timing effect of ACE at 3-5 years of age as well as between 11-13 years of age on bilateral hippocampal volume (Andersen et al., 2008). Thus, recent studies have started to delineate timing effects of ACE pointing to a differential timing effect during preadolescence (about 9-12 years of age) and early adolescence (about 13 years of age) for the development of the amygdala and the hippocampus. The time of pre- and adolescence is characterized by marked changes in brain structure and function, as white and grey matter undergo complex changes, particularly in regions of the frontal cortex that are involved in higher-level cognitive processes (Fuhrmann et al., 2015). Moreover, the limbic system (e.g., the hippocampus and the amygdala) undergo structural and functional maturation during this period (Semple et al., 2013; Toga et al., 2006). Critically, hippocampal, amygdaloidal and cortical regions play a central role in stress reactivity due to their high density of corticosteroid receptors. These receptors detect glucocorticoid stress hormones and regulate the hypothalamic-pituitary-adrenal (HPA) axis (Herman & Cullinan, 1997). As psychological and physiological stressors during pre- and adolescence have a negative impact on the HPA axis (Klein & Romeo, 2013), one may hypothesize that limbic and cortical regions might be especially vulnerable to stress during this time period (Brydges, 2016; Lupien et al., 2009). The aim of the present study was to investigate the impact of retrospectively reported ACE on brain volume in relation to severity of type and timing in a sample of individuals exposed to repeated interpersonal trauma during childhood and adolescence. Severity of type was defined as the extent subjects were exposed to abuse and/or neglect, respectively. To achieve this aim, we first investigated the impact of retrospectively reported *global ACE severity*, *global abuse* and *neglect severity* on volumes of key stress and emotion associated brain structures, i.e., the amygdala, hippocampus, and ACC by pre-defined regions of interest (ROI). We decided to choose the amygdala, the hippocampus, and the ACC as regions of interest, since several studies from human and experimental animal studies demonstrated their sensitivity to early stressful events (Bick & Nelson, 2016; Brydges,

2016; Cross et al., 2017; Nemeroff, 2016). We only concentrated on these three *typical* areas to avoid multiple testing, and thereby the risk of false positive results (Poldrack, 2007). Second we aimed to replicate the findings of timing effects for the amygdala and hippocampus (Andersen et al., 2008; Pechtel et al., 2014) volume during which *time-specific ACE severity* has an impact on brain volume (Andersen et al., 2008; Pechtel et al., 2014). To our knowledge, studies have not so far demonstrated timing effects of the ACC in the context of ACE. Therefore we investigated timing effects within the ACC by exploratory analyses. Third, we were particularly interested if there is an interaction between the timing and the severity of type (*time-specific abuse* and *time-specific neglect severity*) on brain volume. Since the diagnosis of PTSD has also been related to alterations in the amygdala, hippocampus, and ACC (for reviews and meta-analyses see (Hayes et al., 2012b; Shin & Liberzon, 2010; but also Kitayama et al., 2007; Teicher et al., 2012), we took the existence of a PTSD diagnosis in our analyses into account.

3.3 Methods

3.3.1 Sample

The sample consisted of 68 traumatized female participants who reported sexual or physical abuse during childhood and adolescence (inclusion criterion). Fourty-two participants fulfilled the primary diagnosis of posttraumatic stress disorder (PTSD), and 26 participants were free of any mental disorder throughout their life (trauma controls; TC; Rausch et al., 2016). Details on demographic and clinical characteristics, as well as maltreatment exposure history are reported in chapter 3.6.1 and 3.6.2 and Table 3.1-3.5. The study was approved by the Ethical Board II of Heidelberg University, Germany, and was conducted according to the Declaration of Helsinki at the Central Institute of Mental Health in Mannheim. Written informed consent was obtained from the participants after the procedures had been fully explained. All subjects received monetary remuneration for participation in the study.

3.3.2 Maltreatment Exposure

The time course and severity of reported exposure to traumatic events was assessed using an adapted version of the Maltreatment and Abuse Chronology of Exposure Interview (MACE; Isele et al., 2014; Teicher & Parigger, 2015)). The inventory evaluates 10 types of ACE during each year of childhood up to age 17. Within the present investigation, ACE was quantified by a) an averaged MACE severity score indicating ACE across childhood and adolescence, (i.e., global ACE severity), and for each year of life, respectively (i.e., time-specific ACE severity)

(Teicher & Parigger, 2015). The scores range from 0 to 100. To address b) the conceptual framework of active and passive maltreatment (McLaughlin et al., 2014; Sheridan & McLaughlin, 2014), we created two dimensions: Active maltreatment is represented by collapsing the subscales physical and sexual abuse (= abuse), while passive maltreatment is represented by collapsing the subscales physical and emotional neglect (= neglect). The scores have been averaged across childhood and adolescence, i.e., global abuse severity, and global neglect severity, as well as for each year of life, respectively i.e., time-specific abuse severity, and time-specific neglect severity. The neglect and abuse score ranges from 0 to 20 (for details see 3.6.2.1).

3.3.3 Magnetic resonance imaging and image processing

For details on MRI procedure and image processing please see 3.6.2.2 and 3.6.2.3

3.3.4 Statistical Analyses

Repeated measurement analysis of variance (rmANOVA) were applied to investigate differences in reported ACE, abuse, or neglect, respectively, across the life-span, i.e., 3 up to 17 years of age. Pearson correlations were conducted, to investigate the relationship between brain volume (amygdala, hippocampus, ACC) and maltreatment history (i.e., ACE, abuse, and neglect). If necessary, post-hoc comparisons were conducted and adjusted for multiple testing (Bonferroni). Statistical significance was set to $p < .05$. All analyses were performed using SPSS (version 23; SPSS Inc., USA). For further details on statistical analyses regarding the history of maltreatment, clinical, and socio-demographic characteristics see chapter 3.6.3

3.3.5 Analysis of timing effects

To test the presence of timing effects in which exposure to ACE might be more strongly related to alterations in ROI brain volume, we applied random forest regression with conditional interference trees ('cforest' in R package 'party'; (Strobl et al., 2008; Strobl et al., 2009)). Since type and time-specific ACE severity scores were highly intercorrelated (p-values< .030), we applied conditioned random forest regression to identify relevant predictors. This method is advantageous compared to conventional linear models in identifying important predictor variables, as random forest regression considers multicollinearity between predictor variables, while additionally handling a large number of predictor variables (Kuhn & Johnson, 2016; Strobl et al., 2009). We ran the random forest regression with conditional interference trees for

each ROI (GMV, age and TIV corrected, and *z*-transformed). Each random forest model consisted of 500 trees with randomly selected 4 variables available at each split. To define these hyperparameters (i.e., number of trees, number of variable at each split) we systematically varied the number of trees (100–1000), and number of variables selected for decision making (3-5) and tested the model accuracy with respect to the out-of-bag sample (re-defined during each iteration step). To ensure model-stability, the random forest regression was re-iterated 10 times with varying seeds. Please see chapter 3.6.3.4 for details on parameters and details on statistical procedures. The first model investigating differential timing effects of ACE severity on brain volume contained the following predictor variables (i.e. timing model): timing – specific predictors, i.e., ACE severity at each year of life during the recollected lifespan (time-specific ACE severity at 3 – 17 years of age), as well as global predictors, i.e., global ACE severity (averaged severity across age 3 up to 17), and group (presence of a PTSD diagnosis or not). In a second model, the influence of the ACE type in interaction with the timing on brain volume was tested (i.e., type and timing model), i.e., the influence on abuse or neglect during differential time periods on brain volume. This second model contained the following predictor variables: type and timing specific predictors, i.e., time-specific abuse severity, as well as time-specific neglect severity during the recollected lifespan (age 3 - 17), as well as the global predictor variables, i.e., global neglect severity and global abuse severity (averaged neglect and abuse severity across age 3 up to 17), and group.

3.3.6 Data Availability

The datasets generated during and/or analyzed during the current study will be available at https://osf.io/kt7qr/?view_only=16181bf2e6db41cf906f46e192bfc073.

3.4 Results

3.4.1 Global ACE Severity and Regional Brain Volume

In general, regional brain volume was estimated and adjusted with respect to the current age of the participant, respectively. A negative association between global ACE severity across childhood and adolescence and bilateral amygdala volume was observed at a trend level (left: r=-.23, p=.061, right: r=-.216, p=.076, averaged amygdala volume: r=-.23, p=.059). No significant associations were found regarding hippocampus or ACC volume (p-values>.117) (explorative analyses on effects of ACE and PTSD on brain volume can be found in chapter 3.6.4.3).

3.4.2 Severity of ACE Type and Regional Brain Volume

A negative association between global neglect severity across childhood and adolescence and the bilateral amygdala, as well as a trend regarding bilateral hippocampal volume was observed (amygdala: left: *r*=-.26, *p*=.036, right: *r*=-.31, *p*=.011, averaged amygdala volume: *r*=-.29, *p*=.016; Figure 3.1; hippocampus: left: *r*=-.22, *p*=.067, right: *r*=-.22, *p*=.073, averaged hippocampus volume: *r*=-.23, *p*=.064). No significant associations were found regarding ACC volume (*p*-values>.449). No significant associations were observed between global abuse severity across childhood and adolescence, and brain volume (*p*-values>.622).

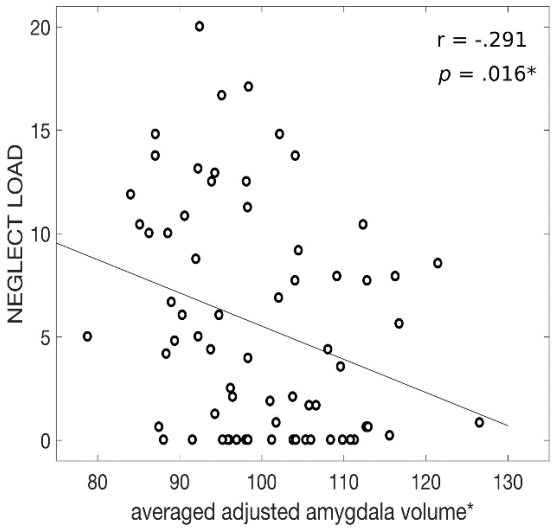


Figure 3.1 Linear regression graphs illustrate the relationship between the global neglect severity during childhood and adolescence and the averaged adjusted amygdala volume.
** brain volume adjusted for current age*

3.4.3 ACE Timing and Regional Brain Volume

Amygdala: Analyses of timing effects revealed that time-specific ACE severity at 13 years of age was an important predictor of both, left, and right adjusted amygdala volumes, while time-specific ACE severity at age 10 was also important in predicting right amygdala volume. Global predictors (i.e., global ACE severity and group) were not detected as important predictors (Figure 3.2 A, for *p*-values of VI scores and trends see Table 3.6). The relationship between the identified age 13 and bilateral amygdala volume, as well as age 10 and right amygdala volume was best described by a linear as compared to a quadratic model: Higher ACE at the identified ages was associated with lower bilateral amygdala volume (for statistics see Table 3.8).

Hippocampus: Time-specific ACE severity at 10, 11, and 13 years of age were important predictors for both, left, and right adjusted hippocampal volumes. Global predictors were not detected as important predictors (Figure 3.2 B, for *p*-values of VI scores and trends see Table

3.6). Illustrative analyses of the type of the relationship between identified ages and hippocampal volume revealed as a trend that the relationship between left hippocampal volume and time-specific ACE severity at 10 was best described by a linear model, while no significant linear or quadratic association was observed regarding time-specific ACE severity at 11 and 13 years of age. With respect to right hippocampal volume and identified ages 10, 11 and 13, a linear model was found to describe the relationship best, suggesting that higher ACE during the latter lifespan is associated with lower bilateral hippocampal volume (Table 3.8) (explorative analyses on ACC volume can be found in chapter 3.6.4.4 and 3.6.4.5).

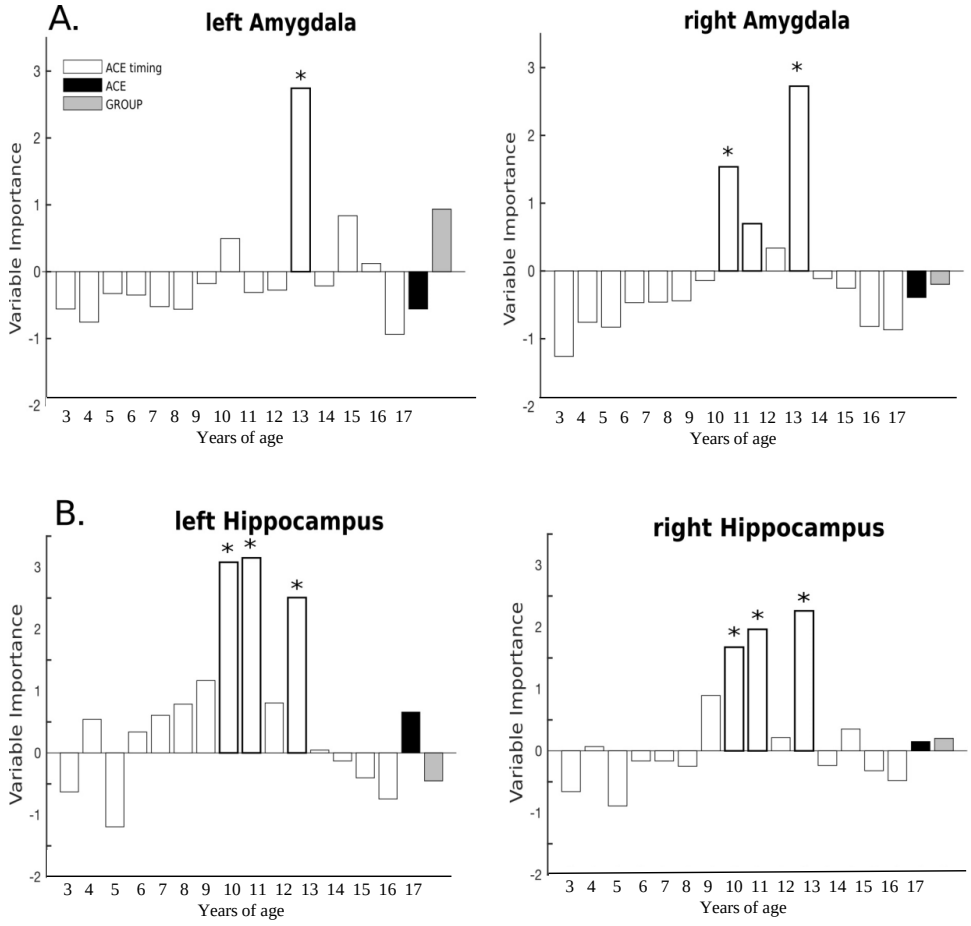


Figure 3.2 Results of random forest regression with conditional interference trees indicating the importance of time-specific ACE severity from 3 up to 17 years of age on bilateral amygdala (A.), and hippocampal volume (B.).
*permutation test: * p < .05; ACE = adverse childhood experience*

3.4.4 Severity of ACE Type x Timing and Regional Brain Volume

Amygdala: Analyses of timing effects revealed that time-specific neglect severity at 14, and 16 years of age were important predictors of left amygdala volume. Time-specific neglect severity at 4, 6, 9, 11, 13, and 14 years of age predicted right adjusted amygdala volume (Figure 3.3 A, for *p*-values of VI scores and trends see Table 3.7). With respect to global predictors, global

neglect severity was found to be an important predictor of right amygdala volume (Table 3.7). Post hoc analyses revealed that the relationship between the bilateral amygdala volume and the identified ages were best described by a linear model, suggesting that higher time-specific neglect severity was associated with lower bilateral amygdala volume (Table 3.8).

Hippocampus: Time-specific abuse at 16 and 17 years of age as well as time-specific neglect severity at 9, 11, 13 and 14 years of age were important predictors of left hippocampal volume. Time-specific neglect severity at 10, 11, and 13 years of age were important predictors of right adjusted hippocampal volume. Global predictors were not detected as important predictors (Figure 3.3 B, for *p*-values of VI scores and trends see Table 3.7). Post hoc analyses revealed that the relationship between the bilateral hippocampus volume and the identified ages were best described by a linear model: While higher time-specific neglect severity was related to a lower bilateral hippocampal volume, higher time-specific abuse severity was related to a greater left hippocampal volume (Table 3.8) (explorative analyses on ACC volume can be found in chapter 3.6.4.4 and 3.6.4.5).

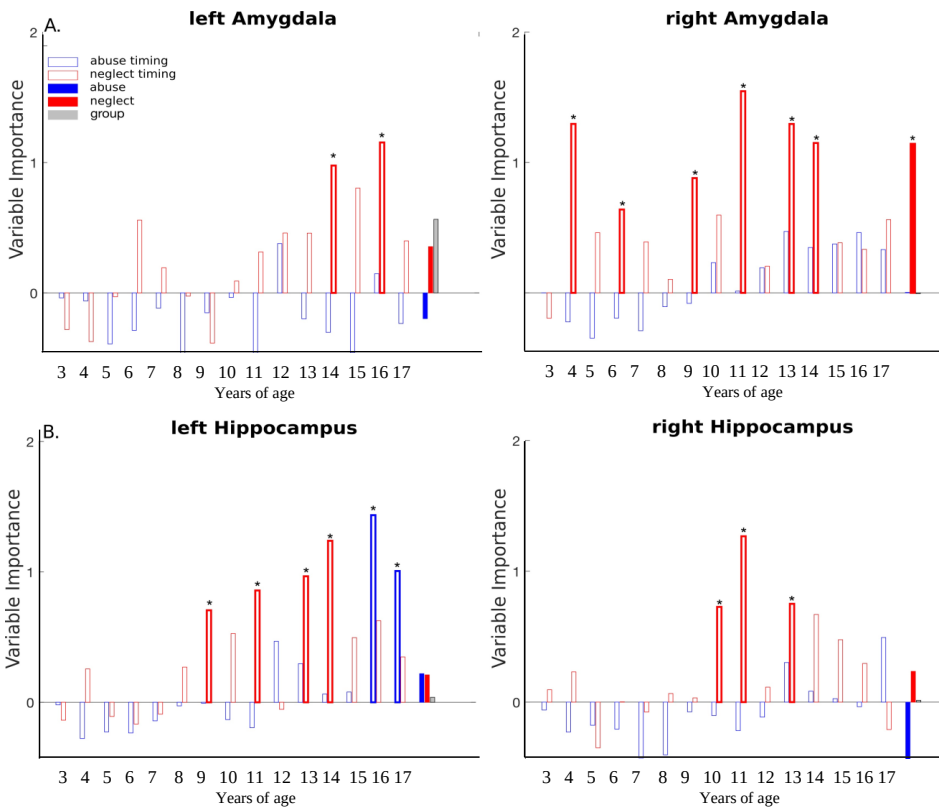


Figure 3.3 Results of random forest regression with conditional interference trees indicating the importance of time-specific neglect and abuse severity from 3 up to 17 years of age on bilateral amygdala (A.), and hippocampal volume (B.).
*permutation test: * p < .05; † < .1*

3.5 Discussion

The present study investigated alterations in brain volume related to retrospectively reported ACE in an adult female traumatized sample with an emphasis on differential effects of severity of type and timing of ACE on brain volume. We found a significant association between global ACE severity and bilateral amygdala volume, while we did not find any association between global ACE severity and hippocampal or ACC volume. The present findings highlight that the application of the dimensions of passive and active maltreatment (McLaughlin et al., 2014; Sheridan & McLaughlin, 2014) can be of importance when investigating effects of ACE on brain volume: The association between global ACE severity and bilateral amygdala volume was driven by the passive maltreatment severity: Higher global neglect severity was associated with smaller bilateral amygdala volume, and at trend level with smaller bilateral hippocampal volume across traumatized individuals, while no such associations were observed for global abuse severity.

Studies so far have revealed heterogeneous findings regarding the direction of the relationship between the severity of neglect and amygdala volume, with some hinting towards a negative relationship (Driessen et al., 2000; Schmahl et al., 2003), while others provided evidence for a positive (Lupien et al., 2011; Mehta et al., 2009; Pechtel et al., 2014) or no association (Sheridan et al., 2012; Zeanah et al., 2003). These heterogeneous findings have been discussed in the context of type of ACE in modulating the relationship, as well as the chronicity and time elapsed since traumatization: Increased amygdala volume was observed primarily in children and adolescent samples with early exposure to emotional and/or physical neglect (but see, Sheridan et al., 2012; Zeanah et al., 2003), while studies reporting reductions in amygdala volume were related to older participants, greater degrees of psychopathology, and exposure to multiple types of abuse during childhood (Teicher & Samson, 2016). Therefore, it has been hypothesized that early exposure to ACE may result in an initial increase in amygdala volume, particularly noticeable during childhood, and/or may also sensitize the amygdala to further stress. The latter may result in a substantial reduction in amygdala volume most noticeable in late adolescence or adulthood (Teicher & Samson, 2016). This argumentation is in line with the present investigation, as our sample included adults with experience of prolonged and severe maltreatment. With regard to the hippocampus, a number of studies found reduced hippocampal volume in adult samples (Teicher et al., 2018), while studies in children or adolescents exposed to neglect have not typically observed changes in hippocampus volume (Sheridan et al., 2012). As observed in the amygdala, it is hypothesized that there may be a silent period between

exposure to maltreatment and discernible neurobiological differences, with observable cross sectional differences becoming fully discernible in later life (Bick & Nelson, 2016). This is further supported by animal studies, showing that early ACE can lead to an increase in certain brain regions immediately following the exposure; while these initial increases can be followed by shrinkage (Bick & Nelson, 2016). In light of heterogeneous findings, capturing maltreatment as an overall measurement, i.e., one score across early life, might be not detailed enough to capture more complex relationships.

Therefore, the present investigation highlights the importance of time-specific ACE severity having an impact on brain development. Timing analyses provided evidence for differential timing effects, during which time-specific ACE severity has an higher impact on brain volume: An effect of timing was observed covering preadolescence (10-11 years of age) and early adolescence (13 years of age), for both bilateral amygdala and hippocampal volume. This fine-grained analysis of differential timing effects matches those observed in previous studies, which also detected timing effects of ACE at the end of childhood and early adolescence (Andersen et al., 2008; Pechtel et al., 2014). Importantly, and besides brain development, similar time windows have been observed for ACE in fostering dissociative symptoms and PTSD symptoms, strengthening the idea that this time of development may be extremely vulnerable to the impact of ACE (Schalinski & Teicher, 2015) (for depressive symptomatology see, Khan et al., 2015). The importance of pre- and early adolescence as a time for the higher impact of ACE is further stressed by studies focusing on brain connectivity patterns across childhood and adolescence: A marked change in amygdala-cortical coupling has been found during the transition from childhood to adolescence, i.e., preadolescence (9-12 years of age), with no connectivity observed in childhood, while a negative coupling has been found at around 11 years of age (Gabard-Durnam et al., 2014).

Narrowing down the influence of timing and additionally focusing on the severity of type in particular, provided a more detailed picture regarding the contribution of neglect in relation to abuse severity across the early life span. We decided to make a first distinction between neglect i.e., deprivation, and abuse i.e., threat, as it is a prominent model of adversity and thus provides a promising first step in delineating particular effects (McLaughlin et al., 2014; Thomason & Marusak, 2017). Distinct consequences have been assumed: Neglect comprises the absence of adaptive inputs, whereas abuse represents harmful experiences compromising the physical integrity (Thomason & Marusak, 2017). Putting these in the context of timing effects, one may hypothesize that both forms may influence neuroanatomical measures differently. Indeed, we did observe type-related effects during different time periods, which were further distinguished

in terms of brain structure: Regarding neglect severity and amygdala volume, vulnerable time windows were detected during preadolescence (10 and 12 years of age) and during adolescence (13 and 14 years of age) for right amygdala volume as well as during later adolescence (age 14 and 16 years of age) for the left amygdala volume. Thus both, pre-, and adolescence and a peak during late adolescence appear to be vulnerable to the severity of neglect. Likewise, we found a differential timing effect of pre-and early adolescence (9-13 years of age), affecting bilateral hippocampal volume in terms of neglect. Contrary to the findings of several studies and meta-analyses (Calem et al., 2017; Riem et al., 2015), we did not find reduced hippocampal volume in subjects after childhood abuse. Our results even show a positive correlation between abuse and hippocampal volume. On the other hand, we found a negative correlation between neglect and hippocampal volume. Possibly due to the overall stronger influence of neglect compared to abuse, we also found an overall negative correlation between ACE severity and hippocampal volume. In earlier studies, the missing distinction between abuse and neglect might have blurred these differential findings.

There are several limitations that should be acknowledged. First, the present analyses of type and timing was based on retrospective reports which are prone to several potential recall biases. Due to the cross-sectional design of our study, we were not able to assess prospective data and objective confirmation of maltreatment (e.g., emergency room records, court filings). The suitability of retrospective measures of childhood maltreatment has recently been investigated and discussed in a meta-analysis by Baldwin et al. (2019) (for further discussion, please see Widom, 2019). The meta-analysis revealed poor agreement between prospective and retrospective measures of childhood maltreatment. Although the authors highlighted that prospective data are generally more advantageous from a scientific perspective to address causality (Widom, 2019), they also highlighted that these results cannot directly be interpreted to indicate poor validity of retrospective measures. Prospective measures are often characterized by a lower sensitivity, as official records often capture only the most severe cases of maltreatment. Moreover, the meta-analysis revealed that the agreement between prospective and retrospective reports is higher in investigations a) applying interviews instead of questionnaires to elicit ACE, b) studying small sample sizes, and c) providing a precise definition of childhood maltreatment. The current investigation did indeed assess childhood maltreatment via the extensive MACE interview, examining 10 different and well defined types of ACE during each year of childhood and adolescence from 3 up to 17 years of age. The interview has been conducted by well-trained and specialized clinical psychologists. The psychometric evaluation of the German version of the MACE provides good support for a valid

and detailed assessment of ACE (see, Isele et al., 2014; Teicher & Parigger, 2015). Moreover, the good test–retest reliability of the MACE provides support that adults are very consistent in their recall of the timing of maltreatment experiences, as such events are often a vital part of an individual's personal narrative (Isele et al., 2014; Teicher & Parigger, 2015). Furthermore, the relatively small sample size in our study allowed an intensive support for participants, resulting in a greater engagement of participants and a detailed retrospective assessment of ACE by diagnosticians. Critically, rapid brain development has been reported during 0-3 years of age, which might leads to pronounced vulnerability towards the impact of ACE during this time. (Kolb & Gibb, 2011). However, verbal autobiographical memories are more accessible from three years of age onward; therefore we decided to investigate the influence of ACE from 3 up to 17 years of age in the present investigation. Moreover, it is important to mention that children reared in maltreating circumstances are also likely to experience a number of ongoing additional stressors, such as poverty, dysfunctional parent-child interaction, which in addition might impact brain development (Cross et al., 2017). In the same context, we further have not assessed protective factors, which possibly might have also an impact of neuroanatomical measures. Adding to this complexity, the impact of ACE on an individual's neurobiology needs further consideration in the context of genetic and epigenetic processes. Although, a detailed consideration of gene-environment interaction is beyond the scope of our study, a particularly relevant area of research are studies of gene-environment interaction of the FKBP5 gene with ACE, which regulates cortisol-binding affinity and the nuclear translocation of the glucocorticoid receptor (for the interested reader see, Binder et al., 2008; Heim & Binder, 2012; Sharma et al., 2016; Watkins et al., 2016). Furthermore, we only included female participants. One has to keep in mind that animal as well as human work on ACE points towards differential effects of ACE in male and females (Teicher et al., 2018; Rucui Yang et al., 2019). Therefore, our results are limited to females and cannot be generalized to male subjects. Finally, we have not assessed behavioral data, which prohibits to analyze potential important relationships between the present structural associations and ACE (e.g., with the hippocampus) and behavioral measures such as memory performance.

Going forward, we urgently need longitudinal and prospective designs including male and female individuals, to better understand the impact of ACE across the entire lifespan on neuroanatomical and behavioral measures. More precisely, future longitudinal studies are urgently needed, focusing on the identification of potential important variables, such as environmental protective factors, objective measurements of maltreatment, gene-environment

interaction that may modulate the relationship of functional and structural brain characteristics and ACE leading to potential cognitive, emotional and behavioral alterations.

Addressing these questions is the aim of our ongoing graduate program "Impact of Adverse Childhood Experiences on Psychosocial and Somatic Conditions across the Lifespan" (GRK2350).

The present study explored the relationship between stress-sensitive brain structures and the effect of severity of type and timing of reported ACE in an adult female traumatized sample. Timing analyses provided evidence for a timing effect covering pre- and early adolescence in influencing amygdala and hippocampal volume. Extending the timing analysis and focusing on the predictive power of ACE type in relation to timing of ACE, we found differential timing effects of abuse and neglect for amygdala and hippocampal volume, respectively. The present results strengthen the idea of a type- and time-sensitive model of ACE in terms of brain volume. This is an important step in gaining a better understanding how early life adversity affects neurodevelopment in terms of providing insight into differential time windows during which ACE has an highly deleterious effect on neuroanatomical measures.

3.6 Supplementary Material

3.6.1 Participants

3.6.1.1 Diagnostic and Consenting Procedures

Clinical diagnoses were assessed by trained diagnosticians using the Structure Clinical Interview for DSM-IV Axis I Disorders (SCID-I; Wittchen et al., 1997), the Clinician Administered PTSD Scale (CAPS; Weathers et al., 2013), and the BPD section of the International Personality Disorder Examination (IPDE; Loranger et al., 1997). Self-report measures included retrospective questionnaires on childhood trauma (Childhood Trauma Questionnaire; CTQ; Bernstein & Fink, 1998), PTSD symptomatology (Davidson Trauma Scale; DTS; Davidson et al., 1997), and severity of depressive mood (Beck Depression Inventory; BDI-II; Hautzinger et al., 2003). Details on demographic data and clinical characteristics of the sample are reported in Table 3.4 and 3.5. The study was approved by the Ethical Board II of Heidelberg University, Germany. It was conducted according to the Declaration of Helsinki at the Central Institute of Mental Health in Mannheim. Written informed consent was obtained from the participants after the procedure had been fully explained. All participants received monetary remuneration for participation in the study.

3.6.1.2 Inclusion and Exclusion Criteria

Participants with PTSD were recruited from a larger randomized controlled trial evaluating dialectical behavioral therapy for PTSD (DRKS00010827). TC subjects were recruited via advertisements in local newspapers, flyers and internet. Exclusion criteria for all participants were metal implants, pregnancy, left-handedness, and claustrophobia. Exclusion criteria for PTSD participants covered current and lifetime schizophrenia or bipolar-I disorder, mental retardation, severe psychopathology, traumatic brain injuries or somatic illness that needs to be treated immediately in another setting (e.g., BMI<16), medical conditions making exposure-based treatment impossible, a suicide attempt within the last two months, and substance dependency with no abstinence within two months prior to the study. Exclusion criteria for the TC sample were any current or previous mental disorder, any psychotherapeutic experience or any intake of psychotropic medication (for more detailed descriptions of the TC sample see: Rausch et al., 2016).

3.6.2 Measures

3.6.2.1 Maltreatment Exposure

The time course and severity of exposure to traumatic events was assessed using an adapted version of the MACE interview (Isele et al., 2014; Teicher & Parigger, 2015). The inventory evaluates ten types of adverse childhood experiences (emotional neglect, physical neglect, parental physical abuse, siblings physical abuse, parental emotional abuse, siblings emotional abuse, sexual abuse, peer abuse, witnessing interparental violence and witnessing violence to siblings) during each year of childhood 3 up to age 17. Scores can be calculated for each ACE type, as well as a total score based on the sum score of all categories. Moreover, the duration, as well as the amount of ACE types experienced during childhood and adolescents can be calculated. With respect to the MACE severity score, test-retest reliability over a time period of 6 month has been found to be very reliable in an US population (Severity: r=.91 [95% CI 0.86-0.94]; p values<.001) (Teicher & Parigger, 2015). Convergent validity scores were found to be good as the MACE severity score correlated 0.74 (95%, CI =0.69– 0.78, $p<10^{-16}$) with the CTQ scores and 0.71 (95%, CI=0.68– 0.73, $p<.001$) an US population (Teicher & Parigger, 2015). The German version has also been tested and the convergent validity scores were found to be comparable (CTQ, r=0.75, p<.001) (Isele et al., 2014). Within the present investigation, ACE was quantified by a) an averaged MACE severity score indicating ACE across childhood

and adolescence, (i.e., *global ACE severity*), and for each year of life, respectively (i.e., *time-specific ACE severity*) (Teicher & Parigger, 2015). The scores range from 0 to 100. To address b) the conceptual framework of active and passive maltreatment (McLaughlin et al., 2014; Sheridan & McLaughlin, 2014), we created two dimensions: Active maltreatment is represented by collapsing the subscales physical and sexual abuse (= *abuse*), while passive maltreatment is represented by collapsing the subscales physical and emotional neglect (= *neglect*). The scores have been averaged across childhood and adolescence, i.e., *global abuse severity*, and *global neglect severity*, as well as for each year of life, respectively i.e., *time-specific abuse severity*, and *time-specific neglect severity*. The neglect and abuse score ranges from 0 to 20.

3.6.2.2 Magnetic Resonance Imaging

Data was collected using a Siemens 3 Tesla TRIO-Scanner (Siemens Medical Solutions, Erlangen, Germany) with a 12-channel head coil. Using three-dimensional magnetization-prepared rapid-acquisition gradient echo (MPRAGE; T1-weighted contrast, TE: 30 ms; TR: 2000 ms; FA=80°; FOV: 192 x 192 mm; number of slices 176, voxel size 1x1x1 mm^3), a high-resolution anatomical scan was acquired for each participant. Head movement artefacts and scanning noise were restricted using head cushions and headphones.

3.6.2.3 Image Processing

Preprocessing of the anatomical T1 images was conducted in Statistical Parametric Mapping (SPM12; http://www.fil.ion.ucl.ac.uk/spm/), and images were segmented into grey matter volume (GM), white matter volume (WM), and cerebrospinal fluid (CSF). Whole brain volume of different compartments was determined by integrating all voxels of GM, WM volume and CSF images. Subsequently, the individual images were normalized to an IXI550 template (McConnell Brain Imaging Centre). The voxel values were modulated with the Jacobian determinant to preserve the amount of change during normalization. Additionally, ROIs, i.e., the bilateral amygdala, hippocampus, and anterior cingulate cortex were defined using the WFU Pickatlas (http://fmri.wfubmc.edu/software/pickatlas). The volume of each ROI was estimated, via the integration of all voxel values within the ROI of the GM image. This was conducted for each subject and the estimated size of each ROI was related to the individuals total intracranial volume (GM+WM+CSF = TIV). Regional volumes corrected for TIV, as well as GM, and WM volume were extracted and exported into SPSS (version 23; SPSS Inc., USA), R (version 3.3.3, and Matlab (Matlab R2016b, Simulink) for statistical analyses. Brain volume estimates were

further corrected for current age, i.e., the current age was regressed out and residuals were z-transformed and taken for further analyses.

3.6.3 Supplemental Statistical Analyses

3.6.3.1 Across Group Analyses

To test, whether the amount of ACE severity differed across the recollected life-span, i.e., 3 up to 17 years of age, a rmANOVA was applied with the within-subject factor '*age'* (3–17). To investigate, whether the amount of traumatization in relation to the type differed across the recollected life-span, a rmANOVA with the within-subject factor age' (3-17) and 'type' (abuse, neglect) was applied. To assess the relationship between global ACE severity, i.e., averaged ACE severity across the recollected life-span, as well as with respect to global ACE type, i.e., global neglect severity and global abuse severity, and brain volume (amygdala, hippocampus, ACC volume corrected for TIV and age), Pearson correlations were conducted.

3.6.3.2 Between Group Analyses

To exploratory test, whether the presence of a PTSD diagnosis has an impact on the observed results, PTSD participants were contrasted to TC participants. Sample characteristics, i.e., sociodemographic variables (age, years of education), clinical characteristics (CTQ, DTS, MACE), were compared with *t* - statistics (Table 3.5). To test whether the groups differed with respect to the amount of ACE severity across the reported life-span, i.e., 3 up to 17 years of age a rmANOVA was applied with the between-subject factor 'group' and the within-subject factor 'age' (age 3 up to 17). To investigate, whether the amount of traumatization in relation to the type differed across the life-span between the groups, a rmANOVA with the between-subject factor 'group', and the within-subject factor 'age' (3-17) and 'type' (abuse, neglect) was applied. Neuroimaging measures with respect to each TIV-adjusted regional ROI were analysed in separate rmANOVA with 'group' as between-subjects factor, and 'hemisphere' as within-subject factor and the covariate 'age'.

3.6.3.3 General Information

For further description of statistical effects in the ANOVA designs, post-hoc comparisons were calculated - if appropriate - by pairwise comparisons (Bonferroni-adjusted for multiple testing). Statistical significance was set to $p<.05$. All analyses were performed using SPSS (version 23; SPSS Inc., USA).

3.6.3.4 Analyses of Timing Effects

To test the presence of timing effects in which exposure to ACE might be related to alterations in ROI brain volume, we applied random forest regression with conditional interference trees ('cforest' in R package 'party' (Strobl et al., 2008; Strobl et al., 2009). This is a machine learning approach, in which an ensemble of unpruned regression trees (forest) is generated. This method is advantageous compared to conventional linear modelling to identify important predictors, as conditioned forest regression considers multicollinearity between predictor variables, does not require specific distribution assumptions or a definition of the relationship between the predictor and response, and can handle a large number of predictors modelling the outcome (Breiman, 2001; Kuhn & Johnson, 2016; Strobl et al., 2009). With respect to the concept how the forest is created, tree building particularly is based on the principle of recursive partitioning, meaning that the feature space (= space spanned by all predictor variables) is recursively partitioned in such that observations with similar response values are grouped (Strobl et al., 2008; Strobl et al., 2009). Thus, smaller groups are generated, which are more homogenous with respect to the outcome. As a single decision tree provides a good fit to the data but is typically a weak predictor in regard to its generalizability, prediction in random forest regression is therefore improved by aggregating trees. Importantly, each tree in the forest is unique, as each tree is generated based on a subset of the entire dataset (bagging), while also the number of predictor variables available at each decision point is restricted. Predictive performance of the model is estimated on the sample that is left out (out-of-bag sample) and thus random forest regression provide an internal estimate, which has found to be highly correlated with either cross-validation or test set estimates (Breiman, 2001; Kuhn & Johnson, 2016). Importance of a given predictor is identified by the variable importance score (VI) (Strobl et al., 2008; Strobl et al., 2009): The score refers to the decrease in model accuracy following the permutation of a given predictor variable. Thereby, if the permutation of a predictor variable causes model accuracy to decrease, it is considered *important*, i.e., it has a higher VI score, while if permuting has no or little impact on model accuracy it is also not considered as *important*. Each random forest model consisted of 500 trees with 4 variables randomly selected for decisions making at each node (Pechtel et al., 2014). To identify, whether the magnitude of VI could have occurred by chance, we applied permutation tests in which the outcome measure (ROI volume) was permuted 1000 times and VI scores for each predictor were assessed (Altmann et al., 2010). *P*-values were determined in terms of the empirical distribution (by the fraction of permutation-based VI scores greater than the not permuted score)

(Altmann et al., 2010; Janitza et al., 2016). To estimate the size of the effect, we calculated the standardized effect (SES; Gotelli & McCabe, 2002) for each VI score. The SES indicates the deviation from the random expectation in standard deviation units, and is defined as follows

$$SES = (I_{obs} - I_{rand}) / \sigma$$

where I_{obs} indicates the observed VI value, I_{rand} indicates the mean of the related, randomly generated VI scores based on the randomized resampling of the observation, and σ indicates the standard deviation of the randomly generated VI scores based on the randomized resampling of the observation. It has to be noted that random forest regression does not provide information on the nature of the relationship, as it is a machine learning algorithm aiming at the detection of relevant predictors, with no a priori assumption of the type of the relationship and thus also considering complex relationships (linear, nonlinear, interaction between predictor variables) . To illustrate the relationship, we therefore examined whether the identified predictor variables and brain volumes might be significantly linearly or quadratically related, while it has to be kept in mind that the relationship may be also more complex. To test the latter, we investigated whether the relationship between the identified ages and ROI volume could better be described by a linear or quadratic model. We set up two general linear models (GLM), one containing a single linear predictor variable, and the second containing an additional quadratic term. To test whether the quadratic term significantly added to the understanding of the relationship between brain volume and identified ages, we tested whether the amount of additional variance explained by the quadratic term (second model) was significant via the F-distribution (Durstewitz, 2017).

3.6.4 Supplemental Results

3.6.4.1 Maltreatment Exposure History

Traumatized subjects reported a history of prolonged traumatization during childhood and adolescence (number of years: M=12.81, SD=3.42), while they were exposed to a variety of ACE types (M=6.01, SD=2.34) (Table 3.4) (for differences between PTSD and TC participants please see chapter 3.6.3.2 and Table 3.5). A detailed characterization of the ACE severity revealed that the amount of traumatization differed across years of age ($F(14,938)=32.19$, $p<.001$, Figure 3.4 A): ACE severity at the beginning, i.e., age 3-6, as well as at the end of the recollected time span, i.e., age 15-17, was lower than during most of the remaining ages (*p*-

values<.045). A significant interaction between severity of type and timing (type x age: $F(14,938)=7.84$, $p<.001$, Figure 3.4 B) revealed that participants reported higher neglect compared to abuse severity at age 3 ($p<.01$) and between 12 and 17 years of age (p's<.035). Abuse severity at the beginning, i.e., age 3-5 of the recollected life span and at the end of the recollected life span, i.e., age 15-17, was lower than for most of the remaining years of age (p-values<.022). With respect to the neglect severity, the reported neglect at the beginning, i.e. age 3-5, as well as the end of the recollected life span, i.e., age 16, and 17 was lower than for most of the remaining years of age (p-values<.039). For detailed comparisons, respectively, please see Table 3.1 (global ACE severity), Table 3.2 (global abuse severity) and Table 3.3 (global neglect severity).

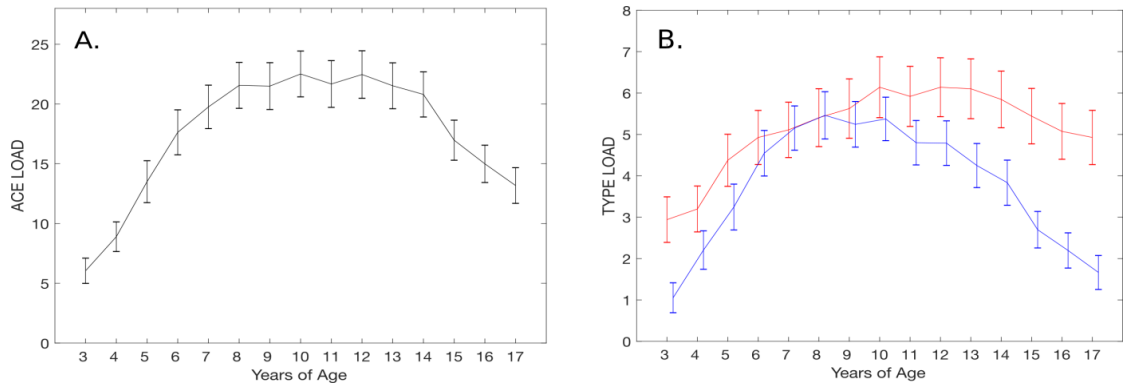


Figure 3.4 Chronology of ACE regarding ACE severity (A.), and severity of ACE type, i.e., abuse (blue), and neglect (red) (B).

3.6.4.2 Maltreatment Exposure History and Clinical Characteristics: Group Comparison

For differences in socio-demographic and clinical characteristics please see Table 3.5. In general, both groups reported exposure to various trauma types (PTSD: M=6.83, SD=2.24; TC: M=4.69, SD=1.85), as well as exposure to maltreatment for a long time period (PTSD: M=13.79, SD=2.76; TC: M=11.23, SD=3.83). Contrasting both groups revealed that PTSD participants reported more trauma types, as well as a longer period of traumatization compared to trauma controls (Table 3.5). Contrasting both groups with respect to the global ACE severity across the recollected lifespan revealed that PTSD compared to TC individuals reported more ACE, while this effect was influenced by years of age (group: $F(1,66)=28.03$, $p<.001$; group x age: $F(14,924)=3.00$, $p<.001$). Taking the severity of type of ACE (global abuse severity vs. global neglect severity) into account, while contrasting both groups revealed that groups differed with respect to global ACE severity in general (group: $F(1,66)=24.78$, $p<.001$), while this was further a trend towards the influence of the type (group x type: $F(1,66)=3.67$, $p=.060$): PTSD participants reported both, more abuse as well as neglect compared to TC participants

(p<.001). While PTSD participants reported more neglect compared to abuse (p=.002), TCs did not differ regarding the recollected amount of abuse compared to neglect (p=.963).

Table 3.1 Bonferroni adjusted post-hoc comparison of the time course of global ACE severity

Age	**3**		**4**		**5**		**6**		**7**		**8**		**9**		**10**		**11**		**12**		**13**		**14**		**15**		**16**		**17**	
	p-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction
3			<.001	4>	<.001	5>	<.001	6>	<.001	7>	<.001	8>	<.001	9>	<.001	10>	<.001	11>	<.001	12>	<.001	13>	<.001	14>	<.001	15>	<.001	16>	<.001	17>
4	<.001	3<			0.09		<.001	6>	<.001	7>	<.001	8>	<.001	9>	<.001	10>	<.001	11>	<.001	12>	<.001	13>	<.001	14>	<.001	15>	0.01	16>	0.25	
5	<.001	3<	0.09				<.001	6>	<.001	7>	<.001	8>	<.001	9>	<.001	10>	<.001	11>	<.001	12>	<.001	13>	<.001	14>	>.9		>.9		>.9	
6	<.001	3<	<.001	4<	<.001	5<			0.03	7>	<.001	8>	0.04	9>	<.001	10>	0.06		0.02	12>	0.36		>.9		>.9		>.9		0.43	
7	<.001	3<	<.001	4<	<.001	5<	0.03	6<			0.46		>.9		0.63		>.9		>.9		>.9		>.9		1.00		0.25		<.001	17<
8	<.001	3<	<.001	4<	<.001	5<	<.001	6<	0.46				>.9		>.9		>.9		>.9		>.9		>.9		0.55		0.02	16<	<.001	17<
9	<.001	3<	<.001	4<	<.001	5<	0.04	6<	>.9		>.9				>.9		>.9		>.9		>.9		>.9		0.26		<.001	16<	<.001	17<
10	<.001	3<	<.001	4<	<.001	5<	<.001	6<	0.63		>.9		>.9				>.9		>.9		>.9		>.9		0.01	15<	<.001	16<	<.001	17<
11	<.001	3<	<.001	4<	<.001	5<	0.06		>.9		>.9		>.9		>.9				>.9		>.9		>.9		0.07		<.001	16<	<.001	17<
12	<.001	3<	<.001	4<	<.001	5<	0.02	6<	>.9		>.9		>.9		>.9		>.9				>.9		>.9		<.001	15<	<.001	16<	<.001	17<
13	<.001	3<	<.001	4<	<.001	5<	0.36		>.9		>.9		>.9		>.9		>.9		>.9				>.9		0.02	15<	<.001	16<	<.001	17<
14	<.001	3<	<.001	4<	<.001	5<	>.9		>.9		>.9		>.9		>.9		>.9		>.9		>.9				0.04	15<	<.001	16<	<.001	17<
15	<.001	3<	<.001	4<	>.9		>.9		>.9		0.55		0.26		0.01	10>	0.07		<.001	12>	0.02	13>	0.04	14>			0.01	16<	<.001	17<
16	<.001	3<	0.01	4<	>.9		>.9		0.25		0.02	8>	<.001	9>	<.001	10>	<.001	11>	<.001	12>	<.001	13>	<.001	14>	0.01	15>			<.001	17<
17	<.001	3<	0.25		>.9		0.43		<.001	7>	<.001	8>	<.001	9>	<.001	10>	<.001	11>	<.001	12>	<.001	13>	<.001	14>	<.001	15>	<.001	16>		

*Note.*Post-hoc *t* tests were performed at a significance level of p< .05 Bonferroni-corrected

Table 3.2 Bonferroni adjusted post-hoc comparison of the time course of global abuse severity

Age	**3**		**4**		**5**		**6**		**7**		**8**		**9**		**10**		**11**		**12**		**13**		**14**		**15**		**16**		**17**	
	p-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction
3			0.03	4>	<.001	5>	<.001	6>	<.001	7>	<.001	8>	<.001	9>	<.001	10>	0.00	11>	0.00	12>	<.001	13>	<.001	14>	0.07		0.92		>.9	
4	0.03	3<			0.88		<.001	6>	<.001	7>	<.001	8>	<.001	9>	<.001	10>	0.01	11>	0.01	12>	0.19		>.9		>.9		>.9		>.9	
5	<.001	3<	0.88				<.001	6>	<.001	7>	<.001	8>	<.001	9>	<.001	10>	0.41		0.58		>.9		>.9		>.9		>.9		0.60	
6	<.001	3<	<.001	4<	<.001	5<			0.31		0.40		>.9		>.9		>.9		>.9		>.9		>.9		0.17		0.02	16<	<.001	17<
7	<.001	3<	<.001	4<	<.001	5<	0.31				>.9		>.9		>.9		>.9		>.9		>.9		>.9		<.001	15<	<.001	16<	<.001	17<
8	<.001	3<	<.001	4<	<.001	5<	0.40		>.9				>.9		>.9		>.9		>.9		>.9		0.22		<.001	15<	<.001	16<	<.001	17<
9	<.001	3<	<.001	4<	<.001	5<	>.9		>.9		>.9				>.9		>.9		>.9		>.9		0.25		<.001	15<	<.001	16<	<.001	17<
10	<.001	3<	<.001	4<	<.001	5<	>.9		>.9		>.9		>.9				>.9		>.9		0.50		0.03	14<	<.001	15<	<.001	16<	<.001	17<
11	<.001	3<	0.01	4<	0.41		>.9		>.9		>.9		>.9		>.9				>.9		>.9		>.9		0.01	15<	<.001	16<	<.001	17<
12	<.001	3<	0.01	4<	0.58		>.9		>.9		>.9		>.9		>.9		>.9				>.9		0.33		0.01	15<	<.001	16<	<.001	17<
13	<.001	3<	0.19		>.9		>.9		>.9		>.9		>.9		0.50		>.9		>.9				>.9		0.26		0.01	16<	<.001	17<
14	<.001	3<	>.9		>.9		>.9		>.9		0.22		0.25		0.03	10>	>.9		0.33		>.9				0.94		0.22		<.001	17<
15	0.07		>.9		>.9		0.17		<.001	7>	<.001	8>	<.001	9>	<.001	10>	0.01	11>	0.01	12>	0.26		0.94				>.9		0.03	17<
16	0.92		>.9		>.9		0.02	6>	<.001	7>	<.001	8>	<.001	9>	<.001	10>	0.00	11>	0.00	12>	0.01	13>	0.22		>.9				0.17	
17	>.9		>.9		0.60		<.001	6>	<.001	7>	<.001	8>	<.001	9>	<.001	10>	0.00	11>	0.00	12>	<.001	13>	<.001	14>	0.03	15>	0.17			

Note. Post-hoc *t* tests were performed at a significance level of p< .05 Bonferroni-corrected

Table 3.3 Bonferroni adjusted post-hoc comparison of the time course of global neglect severity

Age	**3**		**4**		**5**		**6**		**7**		**8**		**9**		**10**		**11**		**12**		**13**		**14**		**15**		**16**		**17**	
	p-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction	*p*-value	direction
3			>.9		0.06		0.02	6>	0.01	7>	0.01	8>	0.00	9>	<.001	10>	<.001	11>	<.001	12>	0.00	13>	<.001	14>	<.001	15>	0.02	16>	0.06	
4	>.9				0.23		0.04	6>	0.02	7>	0.01	8>	0.01	9>	<.001	10>	<.001	11>	<.001	12>	0.00	13>	<.001	14>	0.01	15>	0.07		0.13	
5	0.06		0.23				>.9		>.9		0.54		0.33		0.01	10>	0.06		0.01	12>	0.05	13>	0.24		>.9		>.9		>.9	
6	0.02	3<	0.04	4<	>.9				>.9		>.9		>.9		0.02	10>	0.17		0.02	12>	0.32		>.9		>.9		>.9		>.9	
7	0.01	3<	0.02	4<	>.9		>.9				>.9		>.9		0.16		>.9		0.24		>.9		>.9		>.9		>.9		>.9	
8	0.01	3<	0.01	4<	0.54		>.9		>.9				>.9		0.41		>.9		>.9		>.9		>.9		>.9		>.9		>.9	
9	<.001	3<	0.01	4<	0.33		>.9		>.9		>.9				>.9		>.9		>.9		>.9		>.9		>.9		>.9		>.9	
10	<.001	3<	<.001	4<	0.01	5<	0.02	6<	0.16		0.41		>.9				>.9		>.9		>.9		>.9		>.9		0.78		0.31	
11	<.001	3<	<.001	4<	0.06		0.17		>.9		>.9		>.9		>.9				>.9		>.9		>.9		>.9		>.9		>.9	
12	<.001	3<	<.001	4<	0.01	5<	0.02	6<	0.24		>.9		>.9		>.9		>.9				>.9		>.9		>.9		0.13		0.04	17<
13	<.001	3<	<.001	4<	0.05		0.32		>.9		>.9		>.9		>.9		>.9		>.9				>.9		>.9		0.06		0.01	17<
14	<.001	3<	<.001	4<	0.24		>.9		>.9		>.9		>.9		>.9		>.9		>.9		>.9				>.9		0.14		0.04	17<
15	<.001	3<	0.01	4<	>.9		>.9		>.9		>.9		>.9		>.9		>.9		>.9		>.9		>.9				>.9		0.54	
16	0.02	3<	0.07		>.9		>.9		>.9		>.9		>.9		0.78		>.9		0.13		0.06		0.14		>.9				>.9	
17	0.06		0.13		>.9		>.9		>.9		>.9		>.9		0.31		>.9		0.04	12>	0.01	13>	0.04	14>	0.54		>.9			

Note. Post-hoc *t* tests were performed at a significance level of p< .05 Bonferroni-corrected

Table 3.4 Demographic and clinical variables

	N=68	
Demographics	M	SD
age mean	35.06	(12.30)
years of education	10.88	(1.23)
Clinical Characteristics		
Childhood Trauma Questionnaire (CTQ)		
Total	68.96	(22.29)
Abuse - total	25.15	(9.52)
Neglect - total	27.25	(9.89)
Emotional abuse	16.56	(5.76)
Physical abuse	11.18	(5.71)
Sexual abuse	13.97	(6.99)
Emotional neglect	16.73	(5.74)
Physical neglect	10.52	(4.84)
Davidson Trauma Scale (DTS)		
Total	52.85	(36.21)
Intensity	26.55	(19.11)
Frequency	26.06	(17.68)
Beck Depression Inventory 2 (BDI-II)		
Total	23.95	(18.54)
MACE		
Severity	17.53	(12.64)
Duration	12.81	(3.42)
Types	6.01	(2.33)
MACE Trauma Types		
Neglect	5.14	(5.11)
Abuse	3.77	(3.24)
Emotional Abuse Parents	3.58	(2.42)
Emotional Abuse Siblings	0.69	(1.38)
Physical Abuse Parents	2.84	(2.65)
Physical Abuse Siblings	0.44	(1.22)
Sexual Abuse	0.48	(0.57)
Emotional Neglect	3.50	(3.46)
Physical Neglect	1.64	(2.01)
Peer Abuse	1.43	(1.67)
Witnessing Abuse between Parents	1.09	(1.73)
Witnessing Abuse towards Siblings	1.83	(2.02)
Current Comorbidities	N	(%)
Posttraumatic Stress Disorder	42	(61.67)
Affective Disorder	27	(39.71)
Substance Dependency	0	
Substance Abuse	1	(1.47)
Anxiety Disorder	30	(44.12)
Obsessive Compulsive Disorder	7	(10.29)
Somatization Disorder	3	(4.41)
Eating Disorder	5	(7.35)
Borderline Personality Disorder	20	(29.41)

Table 3.4 (continued)

	N=68	
Psychotropic Medication	N	(%)
SSRI	11	(16.18)
SNRI	10	(14.71)
Tricyclica	5	(7.35)
Other Antidepressants	4	(5.88)
Neuroleptics	8	(11.76)
Anticonvulsants	3	(4.41)
Unmedicated	15	(22.06)

Note. CTQ abuse - total (SD) = CTQ physical abuse + CTQ sexual abuse; CTQ neglect - total (SD) = CTQ emotional neglect + CTQ physical neglect. MACE = Maltreatment and Abuse Chronology of Exposure scale, SD = standard deviation, severity = ACE severity averaged across age 3 up to 17 with respect of all ten types of ACE, duration = averaged years of traumatization reported across age 3 up to 17, types = average numbers of ACE types experienced between age 3 up to 17 (maximal value=10)

Table 3.5 Demographic and clinical variables in PTSD and trauma control subjects

	PTSD		TC		Test-Statistics				
	n=42		n=26		*T*	*df*	*p*		
Demographics	M	(SD)	M	(SD)					
Age mean	37.43	(11.80)	31.23	(12.36)	2.07	66	0.04	*	PTSD>TC
Years of education	10.62	(1.31)	11.31	(0.97)	-2.49	64	0.02	*	TC>PTSD
Clinical Characteristics									
Childhood Trauma questionnaire (CTQ)									
Total	78.49	(21.67)	53.57	(12.75)	5.97	65.89	<.001	*	PTSD>TC
Abuse - total	28.29	(10.12)	20.08	(5.64)	4.29	65.45	<.001	*	PTSD>TC
Neglect - total	31.63	(9.15)	20.18	(6.38)	5.59	66	<.001	*	PTSD>TC
Emotional abuse	18.57	(5.56)	13.31	(4.51)	4.06	66	<.001	*	PTSD>TC
Physical abuse	12.02	(6.51)	9.81	(3.84)	1.77	65.89	.082	†	PTSD(>)TC
Sexual abuse	16.27	(6.78)	10.27	(5.70)	3.76	66	<.001	*	PTSD>TC
Emotional neglect	19.12	(5.13)	12.88	(4.46)	5.12	66	<.001	*	PTSD>TC
Physical neglect	12.51	(4.84)	7.31	(2.65)	5.72	65.23	<.001	*	PTSD>TC
Davidson Trauma Scale (DTS)									
Total	77.73	(18.89)	12.04	(12.80)	15.35	64	<.001	*	PTSD>TC
Intensity	39.42	(10.97)	5.44	(6.43)	15.86	63.94	<.001	*	PTSD>TC
Frequency	38.32	(9.65)	6.73	(6.42)	14.74	65	<.001	*	PTSD>TC
Beck Depression Inventory 2 (BDI-II)									
Total	36.30	(11.66)	4.01	(5.35)	15.51	61.88	<.001	*	PTSD>TC
MACE									
Severity	22.92	(12.69)	8.83	(6.04)	6.160	62.717	<.001	*	PTSD>TC
Duration	13.79	(2.76)	11.23	(3.83)	2.958	41.110	.005	*	PTSD>TC
MULTI	6.83	(2.24)	4.69	(1.85)	4.083	66	<.001	*	PTSD>TC
MACE TRAUMA TYPES									
Neglect overall	7.03	(5.29)	2.10	(2.90)	4.94	65.26	<.001	*	PTSD>TC
Abuse overall	4.82	(3.55)	2.06	(1.60)	4.37	61.52	<.001	*	PTSD>TC
Emotional Abuse Parents	4.32	(2.32)	2.39	(2.12)	3.45	66	.001	*	PTSD>TC
Emotional Abuse Siblings	1.04	(1.63)	.14	(.43)	3.39	49.60	.001	*	PTSD>TC
Physical Abuse Parents	3.52	(2.95)	1.74	(1.55)	3.26	64.66	.002	*	PTSD>TC
Physical Abuse Siblings	.66	(1.50)	.10	(.38)	2.32	49.01	.025	*	PTSD>TC
Sexual Abuse	.64	(.62)	.23	(.34)	3.53	65.27	.001	*	PTSD>TC
Emotional Neglect	4.74	(3.50)	1.50	(2.30)	4.61	65.72	<.001	*	PTSD>TC

Table 3.5 (continued)

	PTSD		TC		Test-Statistics				
	n=42		n=26		*T*	*df*	*p*		
MACE TRAUMA TYPES	M	(SD)	M	(SD)					
Physical Neglect	2.29	(2.24)	0.60	(.90)	4.34	58.68	<.001	*	PTSD>TC
Peer Abuse	1.91	(1.91)	0.66	(.73)	3.82	57.27	<.001	*	PTSD>TC
Witnessing Abuse between Parent	1.51	(2.03)	0.40	(.69)	3.23	54.73	.002	*	PTSD>TC
Witnessing Abuse towards Siblings	2.29	(2.23)	1.07	(1.34)	2.81	65.96	.006	*	PTSD>TC
Current Comorbidities	N	(%)							
Affective Disorder	27	(64.3)							
Substance Dependency	0	(0)							
Substance Abuse	1	(2.4)							
Anxiety Disorder	30	(71.4)							
Obsessive Compulsive Disorder	7	(16.7)							
Somatization Disorder	3	(7.1)							
Eating Disorder	5	(11.9)							
Borderline Personality Disorder	20	(47.6)							
Psychotropic Medication	N	(%)							
SSRI	11	(26.2)							
SNRI	10	(23.8)							
Tricyclica	5	(11.9)							
Other Antidepressants	4	(9.5)							
Neuroleptics	8	(19.1)							
Anticonvulsants	3	(7.1)							
Unmedicated	15	(35.7)							

Note. CTQ abuse - total (SD) = CTQ physical abuse + CTQ sexual abuse; CTQ neglect - total (SD) = CTQ emotional neglect + CTQ physical neglect. MACE = Maltreatment and Abuse Chronology of Exposure scale, SD = standard deviation, severity = ACE severity averaged across age 3 up to 17 with respect of all ten types of ACE, duration = averaged years of traumatization reported across age 3 up to 17, types = average numbers of ACE types experienced between age 3 up to 17 (maximal value=10)

3.6.4.3 Effects of ACE and PTSD on Brain Volume

3.6.4.3.1 Whole Brain Volume Analysis

No significant differences in brain volume were observed.

3.6.4.3.2 Regional Brain Volume Analysis

Amygdala

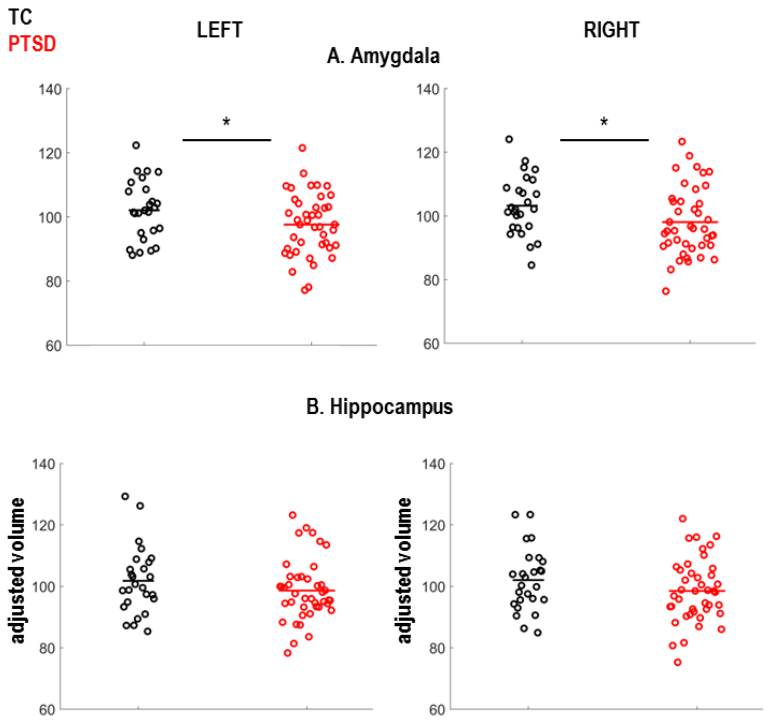
Groups did differ in their amygdala volume irrespective of the hemisphere (group: $F(1,66)=4.89$, $p=.030$, group x hemisphere: $F(1,66)<.01$, $p=.983$, Figure 3.5 A): PTSD subjects had a smaller amygdala volume compared to TC subjects.

Hippocampus

Groups did not differ in hippocampal volume (group: $F(1,66)=1.77$, $p=.189$, group x hemisphere: $F(1,66)=.06$, $p=.816$, Figure 3.5.B).

Anterior Cingulate Cortex

Groups did differ in their ACC volume depending on the hemisphere (group x hemisphere: $F(1,66)=4.65$, $p=.035$; group: $F(1,66)=4.65$, $p=.035$, Figure 3.5C): PTSD subjects had a smaller right ACC volume compared to TC subjects ($p=.035$), while there was a trend towards a smaller left ACC volume in PTSD compared to TC subjects ($p=.064$).



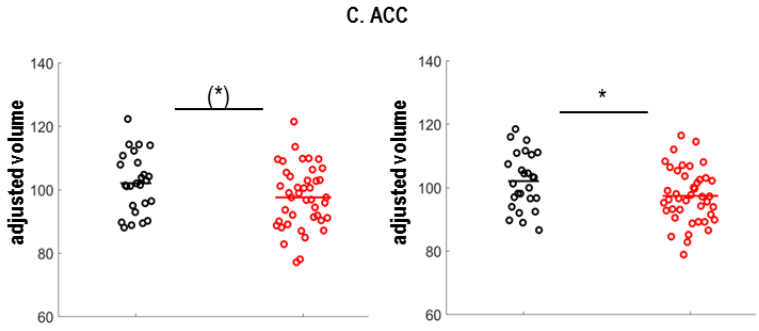


Figure 3.5 Differences in Amygdala (A), Hippocampus (B), and ACC (C) volume adjusted for age in PTSD, and TC subjects

3.6.4.4 Importance of ACE Timing in Predicting Brain Volume

Anterior Cingulate Cortex

Analyses of timing effects revealed that time-specific ACE severity at 10 years of age was important in predicting left, while time-specific ACE severity at 3 years of age was important in predicting right ACC volume (for *p*-values of VI scores and trends see Table 3.6). With respect to global predictors, global ACE severity was found to be an important predictor for left ACC volume, while the predictor group was found to be important in predicting right ACC volume by trend (Table 3.6). Exploring the relationship between ACC volume and the identified ages did not reveal a significant linear, or quadratic relationship (Table 3.8).

3.6.4.5 Importance of ACE Type in Combination with Timing in Predicting Brain Volume

Anterior Cingulate Cortex

Analyses of timing effects revealed that time-specific abuse severity at 7 years of age, and time-specific neglect severity at 3, and 4 years of age were important in predicting left, while time-specific neglect severity at 3, and 4 years of age were important in predicting right ACC volume (for *p*-values of VI scores and trends see Table 3.7). With respect to global predictors, global abuse severity was found to be an important predictor on a marginal significant level for left, and global neglect severity for right ACC volume, scores while the predictor group was found to be important in predicting right ACC volume only (Table 3.7). Exploring the relationship between ACC volume and the identified ages did not reveal a significant linear, or quadratic relationship (Table 3.8).

3.6.4.6 Importance of the Severity of a specific ACE Type in Combination with Timing in Predicting Brain Volume

To exploratory investigate whether the observed importance of neglect in predicting amygdala and hippocampal volume during specific time periods was mainly related to the inclusion of the severity of abuse into the type x timing model, we additional run separate random forest regression analyses including either a) the severity of neglect during specific time periods, or b) the severity of abuse during specific time periods as predictor variables in predicting amygdala or hippocampal volume.

3.6.4.6.1 Abuse

Amygdala Volume

Analyses of timing effects revealed no time-specific ACE severity was important in predicting left, or right amygdala volume (for *p*-values of VI scores and trends see Table 3.9). With respect to global predictors, the predictor group was found to be important in predicting both left, and right amygdala volume (Table 3.9, Figure 3.6 A).

Hippocampus Volume

Analyses of timing effects revealed that time-specific abuse severity at age 16 was important in predicting left hippocampal volume (for *p*-values of VI scores and trends see Table 3.9). With respect to global predictors, the predictor group was found to be important in predicting right hippocampus volume (Table 3.9, Figure 3.6 B).

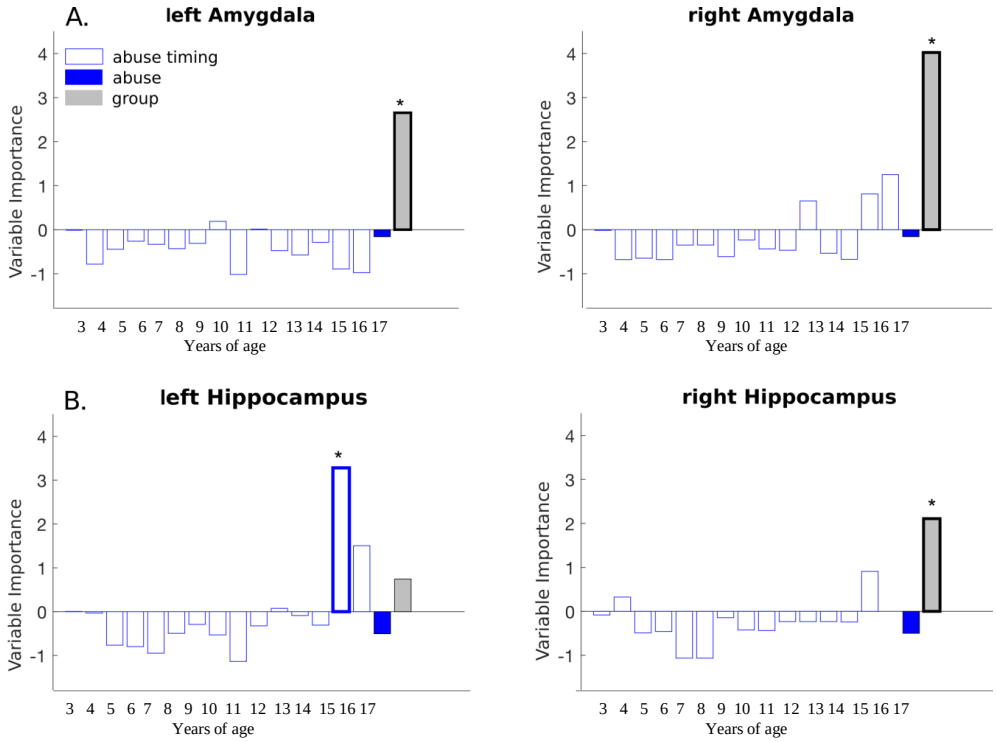


Figure 3.6 Results of random forest regression with conditional interference trees indicating the importance of time-specific abuse severity from 3 up to 17 years of age on bilateral amygdala (A.), and hippocampal volume (B.).
*permutation test: * $p < .05$; † $< .1$*

3.6.4.6.2 Neglect

Amygdala Volume

Analyses of timing effects revealed that time-specific neglect severity at age 11 was important in predicting right amygdala volume (for *p*-values of VI scores and trends see Table 3.9). With respect to global predictors, none of the latter were found to be important in predicting left or right amygdala volume (Table 3.9, Figure 3.7 A).

Hippocampus Volume

Analyses of timing effects revealed that time-specific neglect severity at age 10 was important in predicting right hippocampus volume (for *p*-values of VI scores and trends see Table 3.9). With respect to global predictors, none of the latter were found to be important in predicting left or right hippocampal volume (Table 3.9, Figure 3.7 B).

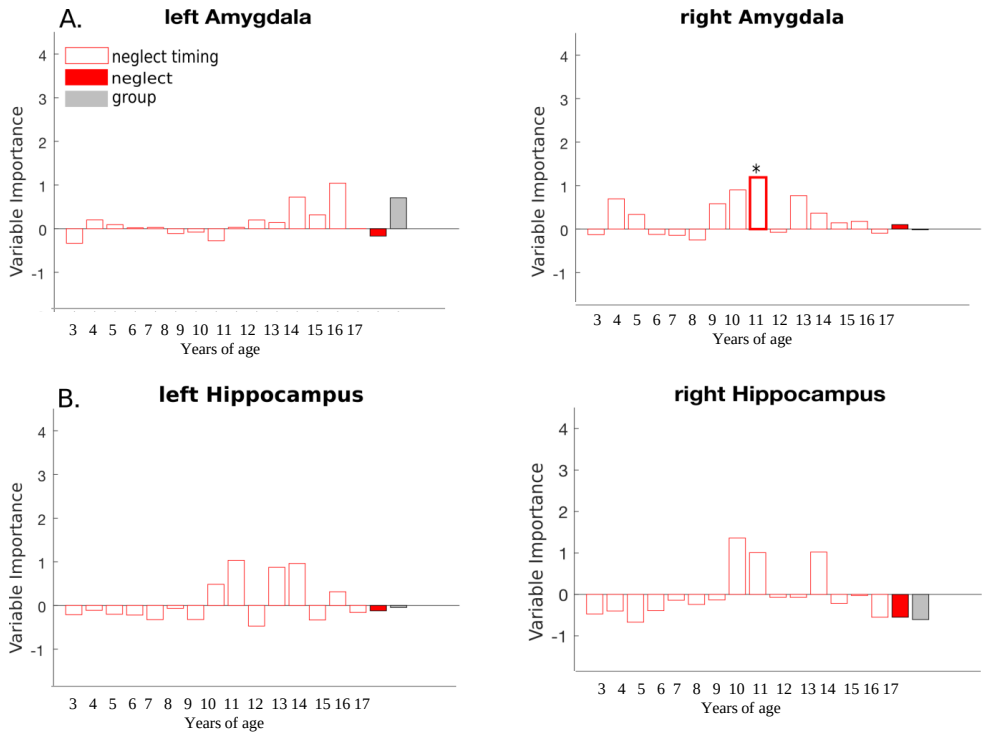


Figure 3.7 Results of random forest regression with conditional interference trees indicating the importance of time-specific neglect severity from 3 up to 17 years of age on bilateral amygdala (A.), and hippocampal volume (B.).
*permutation test: * $p < .05$; † $< .1$*

Table 3.6 Analyses of timing effects on ROI volume using random forest regression with conditional interference trees indicating significant of identified predictors and fit based on randomized resampling.

Region	Predictor	Peak VIa	*p*	SES	
Amygdala					
left	13	2.74	.024	3.44	*
left	global severity	-0.56	.931	-	ns
left	group	0.93	.116	-	ns
right	10	1.54	.048	2.99	*
right	13	2.73	.015	3.99	*
right	global severity	-0.39	.791	-	ns
right	group	-0.19	.411	-	ns
Hippocampus					
left	9	1.17	.061	0.88	†
left	10	3.08	.008	4.12	*
left	11	3.15	.010	3.71	*
left	13	2.51	.021	3.41	*
left	global severity	0.66	.103	-	ns
left	group	-0.45	.621	-	ns
right	9	0.89	.087	1.31	†
right	10	1.67	.033	2.29	*
right	11	1.96	.025	2.23	*
right	13	2.26	.016	2.79	*
right	global severity	0.15	.308	-	ns
right	group	0.20	.204	-	ns
ACC					
left	4	1.28	.096	1.38	†

Table 3.6 (continued)

Region	Predictor	Peak VIa	*p*	SES	
ACC					
left	8	0.89	.084	0.89	†
left	9	0.76	.098	1.62	†
left	10	1.18	.049	1.99	*
left	global severity	1.14	.019	2.10	*
left	group	0.52	.169	-	ns
right	3	2.15	.039	2.95	*
right	4	1.37	.061	1.69	†
right	9	0.73	.094	0.77	†
right	10	0.94	.066	1.78	†
right	11	0.90	.066	1.56	†
right	global severity	0.34	.150	-	ns
right	group	1.43	.056	1.05	†

Note.* p< .05, †< .1, ACC = anterior cingulate cortex, SES = standardized effect size, VI = Variable importance indicating the decrease in model accuracy, ns = not significant, ROI = region of interest

Table 3.7 Interaction between differential time effects and ACE type, i.e., time-specific neglect severity and time-specific abuse severity, on ROI volume using random forest regression with conditional interference trees indicating significant of identified predictors based on randomized resampling.

Region	Predictor	Peak VI	*p*	SES	
Amygdala					
left	N 6	0.56	.063	1.16	†
left	N 12	0.46	.094	1.13	†
left	N 13	0.46	.090	0.49	†
left	N 14	0.98	.036	3.12	*
left	N15	0.80	.059	1.55	†
left	N 16	1.15	.030	3.58	*
left	N 17	.039	.099	1.09	†
left	neglect global	0.36	.110	-	ns
left	abuse global	-.19	.662	-	ns
left	group	0.56	.110	-	ns
right	N 4	1.29	.029	2.65	*
right	N 5	0.46	.089	1.19	†
right	N 6	0.64	.049	0.92	*
right	N 9	0.88	.041	2.16	*
right	N 10	0.59	.071	1.17	†
right	N 11	1.54	.006	2.66	*
right	N 13	1.29	.021	2.88	*
right	N 14	1.15	.014	2.16	*
right	N 17	0.57	.074	1.29	†
right	neglect global	1.14	.013	2.27	*
right	abuse global	<0.01	.366	-	ns
right	group	<0.01	.293	-	ns
Hippocampus					
left	A 16	1.43	.030	3.62	*
left	A 17	1.01	.040	1.76	*
left	N 9	0.70	.044	1.29	*
left	N 10	0.53	.085	1.41	†
left	N 11	0.86	.037	1.88	*
left	N 13	0.97	.028	1.89	*
left	N 14	1.24	.017	2.16	*
left	N 16	0.63	.064	1.26	†
left	neglect global	0.21	.203	-	ns

Table 3.7 (continued)

Region	Predictor	Peak VI	*p*	SES	
Hippocampus					
left	abuse global	0.22	.188	-	ns
left	group	0.04	.249	-	ns
right	N 10	0.72	.046	0.81	*
right	N 11	1.27	.012	2.63	*
right	N 13	0.75	.028	2.11	*
right	N 14	0.67	.061	1.59	†
right	N 15	0.47	.098	0.03	†
right	neglect global	0.24	.165	-	ns
right	abuse global	-0.48	.933	-	ns
right	group	0.01	.262	-	ns
ACC					
left	A 7	1.07	.041	1.21	*
left	A 8	0.78	.065	1.03	†
left	A 14	0.54	.090	0.54	†
left	N 3	0.88	.042	1.34	*
left	N 4	1.61	.009	3.99	*
left	N 5	0.41	.098	2.51	†
left	N 7	0.34	.095	1.28	†
left	neglect global	0.07	.311	-	ns
left	abuse global	0.59	.080	1.77	†
left	group	0.58	.109	-	ns
right	N 3	0.84	.031	2.62	*
right	N 4	1.19	.011	3.36	*
right	N 5	0.45	.070	1.87	†
right	N 8	0.35	.079	0.88	†
right	N 10	0.35	.088	0.56	†
right	neglect global	0.67	.027	1.55	*
right	abuse global	0.26	.146	-	ns
right	group	0.91	.049	2.54	*

Note. * p< .05, †< .1, ACC = anterior cingulate cortex, SES = standardized effect size, N = neglect, A = abuse, VI = Variable importance indicating the decrease in model accuracy, ns = not significant, ROI = region of interest

Table 3.8 Results of generalized linear model regression for severity of type and timing related variables in predicting amygdala, hippocampus and ACC volume.

	Model	Linear Term			Quadratic Term			Model Comparison	
		beta-value	*T-value*	*p*	*beta-value*	*T-value*	*p*	*F-value*	*p*
Left Amygdala									
ACE 13	**linear**	-.0001	-2.04	.045	--	--	--	.02	.885
	quadratic	-.0001	-.81	.422	<.001	.15	.884		
Neglect 14	**linear**	-.0003	-2.20	.031	--	--	--	.75	.390
	quadratic	-.0007	-1.49	.140	<.001	.87	.386		
Neglect 16	**linear**	-.0003	-2.30	.024	--	--	--	.19	.665
	quadratic	-.0005	-1.13	.261	<.001	.44	.663		
Right Amygdala									
ACE 10	**linear**	-.0001	-2.02	.048	--	--	--	1.19	.279
	quadratic	.0001	0.39	.696	<.001	-1.09	.276		
ACE 13	**linear**	-.0001	-1.92	.058	--	--	--	.002	.964
	quadratic	-.0001	-.67	.504	<.001	.05	.963		
Neglect 4	**linear**	-.0005	-2.58	.012	--	--	--	<.001	.990
	quadratic	-.0005	-0.97	.335	<.001	0.01	.990		
Neglect 6	**linear**	-.0004	-2.31	.024	--	--	--	.72	.399
	quadratic	-.0008	-1.58	.118	<.001	0.86	.395		

Table 3.8 (continued)

	Model	Linear Term			Quadratic Term			Model Comparison	
		beta-value	*T-value*	*p*	*beta-value*	*T-value*	*p*	*F-value*	*p*
Right Amygdala									
Neglect 9	**linear**	-.0004	-2.60	.011	--	--	--	.45	.505
	quadratic	-.0007	-1.49	.139	<.001	0.68	.502		
Neglect 11	**linear**	-.0004	-2.68	.009	--	--	--	.77	.383
	quadratic	-.0008	-1.69	.096	<.001	.89	.379		
Neglect 13	**linear**	-.0004	-2.62	.011	--	--	--	.40	.527
	quadratic	-.0007	-1.42	.160	<.001	.64	.524		
Neglect 14	**linear**	-.0004	-2.52	.014	--	--	--	.25	.616
	quadratic	-.0006	-1.24	.219	<.001	.51	.613		
Left Hippocampus									
ACE 10	linear	-.0003	-1.69	.096	--	--	--	4.33	.041
	quadratic	.0007	1.43	.158	<.001	-2.09	.039		
ACE 11	linear	-.0002	-1.49	.139	--	--	--	2.75	.102
	quadratic	.0005	1.07	.289	<.001	-1.67	.099		
ACE 13	linear	-.0002	-1.56	.124	--	--	--	1.04	.312
	quadratic	.0002	.46	.650	<.001	-1.03	.307		
Neglect 9	**linear**	-.0007	-1.74	.087	--	--	--	.005	.939
	quadratic	-.0006	-.49	.622	<.001	-.08	.939		
Neglect 11	**linear**	-.0008	-2.68	.009	--	--	--	.77	.383
	quadratic	-.0016	-1.69	.096	<.001	.89	.379		
Neglect 13	**linear**	-.0009	-2.24	.029	--	--	--	.08	.775
	quadratic	-.0012	-.97	.338	<.001	.29	.773		
Neglect 14	**linear**	-.0008	-1.97	.053	--	--	--	.03	.866
	quadratic	-.0011	-.75	.455	<.001	.17	.865		
Abuse 16	**linear**	.0017	2.51	.015	--	--	--	.32	.577
	quadratic	.0027	1.37	.176	-.0001	-.57	.574		
Abuse 17	**linear**	.0013	1.78	.079	--	--	--	.02	.902
	quadratic	-.0008	.38	.706	<.001	.12	.901		
Right Hippocampus									
ACE 10	**linear**	-.0003	-1.94	.057	--	--	--	1.68	.199
	quadratic	.0003	.61	.544	<.001	-1.31	.196		
ACE 11	**linear**	-.0002	-1.74	.087	--	--	--	.54	.465
	quadratic	.0001	.12	.907	<.001	.74	.462		
ACE 13	**linear**	-.0003	-1.75	.085	--	--	--	.01	.911
	quadratic	.0002	-.47	.642	<.001	-.11	.911		
Neglect 10	**linear**	-.0008	-2.04	.046	--	--	--	.62	.434
	quadratic	-.0016	-1.43	.159	.0001	.73	.430		
Neglect 11	**linear**	-.0008	-2.02	.047	--	--	--	.99	.323
	quadratic	-.0019	-1.59	.116	.0001	1.00	.319		
Neglect 13	**linear**	-.0008	-2.18	.033	--	--	--	.19	.666
	quadratic	-.0013	-1.09	.281	<.001	.44	.663		
Left ACC									
ACE 10	linear	<.001	-.35	.725	--	--	--	3.25	.076
	quadratic	.0015	1.61	.113	<.001	-1.81	.074		
Neglect 3	**linear**	-.0017	-1.69	.095	--	--	--	.99	.325
	quadratic	<.001	.30	.764	<.001	-1.00	.321		
Neglect 4	**linear**	-.0018	-1.77	.081	--	--	--	.94	.335
	quadratic	<.001	.24	.809	<.001	-.98	.331		
Abuse 7	linear	.0007	.67	.506	--	--	--	.479	.491
	quadratic	-.0010	-.37	.711	.0001	.69	.488		
Right ACC									
ACE 3	linear	-.1724	-1.40	.166	--	--	--	.002	.964
	quadratic	-.1557	-.41	.685	-.0007	-.05	.963		
Neglect 3	**linear**	-.4244	-1.81	.074	--	--	--	1.38	.245
	quadratic	.2685	.42	.672	-.0512	-1.18	.241		

Table 3.8 (continued)

	Model	Linear Term			Quadratic Term			Model Comparison	
		beta-value	*T-value*	*p*	*beta-value*	*T-value*	*p*	*F-value*	*p*
Right ACC									
Neglect 4	linear	-.3749	-1.61	.113	--	--	--	1.85	.178
	quadratic	.4117	.66	.508	-.0585	-1.34	.174		

Note.* p<.05, †<.1, bold notation highlights favoured model, ACC = anterior cingulate cortext.

Table 3.9 Analyses of differential timing effects and severity of ACE type, respectively, i.e., time-specific neglect severity and time-specific abuse severity, on ROI volume using random forest regression with conditional interference trees indicating significant of identified predictors based on randomized resampling.

Region	Predictor	Peak VI	*p*	SES	
Amygdala					
abuse					
left	group	2.65	.041	2.25	*
right	17	1.25	.073	1.29	†
right	group	4.02	.019	2.97	*
neglect					
left	16	1.04	.069	1.53	†
right	10	0.90	.085	0.78	†
right	11	1.19	.049	1.66	*
Hippocampus					
abuse					
left	16	3.28	.020	3.31	*
left	17	1.50	.054	1.86	†
right	group	2.11	.045	2.01	*
neglect					
left	11	1.03	.057	1.66	†
left	13	0.87	.090	1.30	†
left	14	0.96	.072	1.36	†
right	10	1.36	.046	1.91	*
right	11	1.01	.064	1.50	†
right	14	1.02	.070	1.40	†

Note.* p<.05, †<.1, VI = Variable importance indicating the decrease in model accuracy, SES = standardized effect size

4 STUDY III: PSYCHOTHERAPY CAN NORMALIZE NEUROCOGNITIVE ALTERATIONS IN COMPLEX POSTTRAUMATIC STRESS DISORDER RELATED TO CHILD MALTREATMENT

An adapted version of this chapter has been submitted as 'Herzog, J. I., Niedtfeld, I., Priebe, K., J., Mueller-Engelmann, M., Steil, R., Kleindienst, N., Bohus, M., Schmahl, C. (subm). Psychotherapy can Normalize Neurocognitive Alterations in Complex Posttraumatic stress disorder related to Child Maltreatment'.

4.1 Abstract

Functional neuroimaging (fMRI) studies in patients with posttraumatic stress disorder (PTSD) have shown impaired inhibitory control leading to enhanced emotional interference. This was demonstrated by increased Stroop interference, coupled with altered limbic and prefrontal brain activation during the processing of threatening stimuli. There is preliminary evidence that treatment can normalize these behavioral and neural activation patterns in patients with complex presentations of PTSD (cPTSD). Thirty-five female patients with cPTSD related to child maltreatment were randomly assigned to Dialectical Behavior Therapy for PTSD or Cognitive Processing Therapy. They underwent diagnostic evaluation and fMRI scanning before and after 12 months of psychotherapeutic treatment while completing an emotional and classic Stroop type paradigm. After 12 months of treatment, cPTSD patients showed improved behavioral performance (faster reaction times and less errors), as well as decreased activation in the amygdala, insula, dorsolateral prefrontal cortex and dorsal anterior cingulate cortex during the processing of trauma-related words compared to neutral and negative words and compared to pretreatment. These results can be interpreted as a "normalization" of behavioral and neural patterns and might suggest that less emotional reactivity/interference towards trauma-related cues might potentially reflect less need for recruitment of prefrontal regions in order to compensate for previously increased emotional reactivity.

4.2 Introduction

Child maltreatment (CM) is highly prevalent worldwide (Koenen et al., 2017; Sethi et al., 2013) and is correlated to higher rates of posttraumatic stress disorder (PTSD) than other types of trauma (Kessler et al., 2017). The development of PTSD in the aftermath of prolonged CM is often associated with severe co-occurring psychopathology, such as borderline personality disorder (BPD) features (Pagura et al., 2010; Yen et al., 2002) like dissociative symptoms, non-

suicidal self-injury (NSSI) and emotion regulation problems. ICD-11 (World Health Organization, 2018) has included complex PTSD (cPTSD) as a new diagnosis, which is defined by PTSD symptoms plus disturbances in emotion regulation, self-concept, and interpersonal relationships (Brewin, 2019; Karatzias et al., 2017; Marinova & Maercker, 2015; Powers et al., 2017). Building on a large body of behavioral and functional magnetic resonance imaging (fMRI) studies, contemporary etiological models of PTSD theorize that PTSD is characterized by increased emotional interference, and dysfunctions in inhibitory control of emotions (DeGutis et al., 2015; Reinhard et al., 2017; Swick et al., 2012). These may lead to increased attentional and emotional reactivity towards emotional (potentially threatening) stimuli, aggravating the core symptoms of (c)PTSD (e.g., hypervigilance, intrusive thoughts, flashbacks and affective dysregulation) (for review see, Hayes et al., 2012a).

At the neural level, it was postulated that these impairments point to an imbalance in fronto-limbic brain circuits, (also referred to as dysfunctions in the 'salience and fronto-parietal network'; Cole et al., 2014; Marek & Dosenbach, 2018). Those were further characterized as heightened reactivity of limbic regions (amygdala, insula) and diminished activation in prefrontal regions associated with cognitive and inhibitory control (dorsal anterior cingulate cortex [dACC], dorsolateral prefrontal cortex [dlPFC], and ventromedial prefrontal cortex [vmPFC]) (Hughes & Shin, 2011; Rauch et al., 2006; Sheynin & Liberzon, 2017). Experimental paradigms, in which participants are required to perform a cognitive task during the presentation of emotional and trauma-related stimuli, allow insight into the underlying mechanisms of emotional interference and inhibitory control, such as the Classic (cStroop) and Emotional Stroop Tasks (eStroop). In the eStroop task, a variation of the cStroop, the participant has to name the color of a word while ignoring the semantic meaning of the word. Reaction times are typically longer for emotionally charged words compared to neutral words. These eStroop effects differ from inherent semantic or response conflict occurring for incongruent trials in the standard cStroop task (e.g., *RED* written in blue), but rather reflect that emotionally charged words tend to attract attention, especially when they are relevant to the individual's history (e.g., the word *GUN* for a veteran) (Okon-Singer et al., 2015; Pessoa & Ungerleider, 2004; Song et al., 2017). Numerous studies have found that patients with PTSD exhibit impaired performance in both the cStroop (Flaks et al., 2014) and eStroop, as compared to healthy individuals with trauma history (Khanna et al., 2015; McNally et al., 1990) and without trauma history (Thomaes et al., 2012; Wingenfeld et al., 2011). Further, they were found to exhibit increased amygdala responses to emotional words (e.g., White et al., 2015) and disrupted

recruitment of prefrontal regions that are associated with cognitive control, especially in the presence of emotional distractors (Blair et al., 2013; New et al., 2009).

Several psychotherapeutic approaches have been developed for the treatment of PTSD. According to current guidelines (American Psychological Association, 2017; International Society for Traumatic Stress Studies, 2019a; Schäfer et al., 2019), treatments of choice for adult patients with PTSD are Cognitive Behavioral Therapy (CBT) (Monson & Shnaider, 2014), Cognitive Processing Therapy (CPT) (Resick et al., 2016), Cognitive Therapy (CT) (Ehlers et al., 2014; Ehlers & Clark, 2000), Prolonged Exposure Therapy (PE) (Foa et al., 2019) and Eye Movement Desensitization and Reprocessing (EMDR) (Shapiro, 2018). Although these treatments have been shown to be efficacious in treating adults with PTSD in general (Watkins et al., 2018), several meta-analyses demonstrated substantially lower effect sizes in cPTSD patients related to CM (g=0.72) (Ehring et al., 2014), when compared to PTSD related to mixed traumatic events (ranging from g=1.08 to 1.40) (Cusack et al., 2016), indicating poorer treatment response (Karatzias et al., 2019). In response to the inclusion of cPTSD as a new diagnostic entity in ICD-11 (Brewin, 2019), international guidelines recommend to add interventions, in a phase-based or integrative treatment, which directly addresses problems that are particularly problematic among those with cPTSD (e.g., emotion dysregulation, negative self-concept and disturbances in relationships) (International Society for Traumatic Stress Studies, 2019b; Schäfer et al., 2019). A phase-based program is Dialectical Behavioral Therapy for PTSD (DBT-PTSD), which was established to meet the specific needs of patients with a history of CM and cPTSD (for further information see, Bohus et al., 2019; Steil et al., 2011). The evaluation of DBT-PTSD revealed significant PTSD symptom reduction under residential (ranging from g=1.22 to 1.27) (Bohus et al., 2013; Steil et al., 2011) as well as under outpatient conditions (Cohen's d=1.50) (Steil et al., 2018). A second psychotherapeutic program, which has been shown to be highly efficacious in treating PTSD patients with a history of CM (Chard, 2005), is CPT (Asmundson et al., 2019; Resick et al., 2008; Resick et al., 2002; Resick et al., 2017). In a recent randomized clinical trial (RCT) under outpatient condition, our group compared the efficacy of DBT-PTSD against CPT**:** Intent-to-treat analysis revealed significantly improved PTSD symptoms for both treatments (Cohen's d=1.35 for DBT-PTSD and Cohen's d=0.98 for CPT) and a small but significant superiority of DBT-PTSD (group difference: 4.82, [95% CI, 0.67- 8.96], p=.02; d=0.33) (Bohus et al., 2020).

Several studies have investigated the association between psychotherapy and the improvement of neuropsychological functions in PTSD (for psychopharmacological interventions on

executive functions in PTSD see, Fani et al., 2009; Flanagan et al., 2018; Koch et al., 2019; Vermetten et al., 2003). One study has demonstrated improved eStroop performance in PTSD patients compared to healthy controls after required (on average) four treatment sessions of EMDR therapy (El Khoury-Malhame et al., 2011). A further study has shown improvements in sub-domains of executive functions with a trend towards overall improvement in executive function after ten sessions of trauma-focused (including CPT and PE) psychotherapy (Walter et al., 2010). In a recent RCT, comparing the efficiency of brief eclectic psychotherapy (BEP) and EMDR, the authors found that both treatments improved neuropsychological functioning in verbal learning and memory as well as information processing speed and executive functioning (Nijdam et al., 2018). However, others did not find effects of psychological treatment on executive functioning in patients with PTSD (e.g., Devineni et al., 2004).

Other studies examined neurobiological effects of psychotherapy in adult-trauma PTSD patients. Using different paradigms to elicit negative affect (script-driven imagery, emotional faces, emotional pictures) before and after treatment, most studies found reduced activation of the salience network (amygdala, insula, hippocampus, ventral ACC), and increased activation within the executive network (rostral ACC, dlPFC) after various types of psychotherapy (Abdallah et al., 2019; Dickie et al., 2011; Felmingham et al., 2007; Levin et al., 1999; Lindauer et al., 2008; Peres et al., 2011; Peres et al., 2007; Simmons et al., 2013; van Rooij et al., 2016). Investigating inhibitory control with Stroop and Go/noGo paradigms, two studies found evidence for increased dACC activation and decreased amygdala activation together with symptom improvement after treatment (Roy et al., 2014; Roy et al., 2010).

Thomaes et al. (2012) were the first who studied treatment effects of a cognitive behavioral stabilizing group treatment in addition to treatment as usual (TAU) vs. TAU only in cPTSD related to CM during fMRI. Before treatment, cPTSD patients showed increased activation in the anterior insula and dACC while completing a Stroop-type paradigm. After treatment, patients showed diminished activation in the superior frontal cortex, dACC and insula, with no change in amygdala activation (Thomaes et al., 2012). Even though this study provides first evidence of neurobiological treatment effects in cPTSD after CM, the results are in clear need of replication. Notwithstanding, there is no study investigating neurobiological treatment effects of trauma-focused outpatient treatment over a longer period in this severely affected group of patients with cPTSD related to CM. Consequently, the goal of this study was to examine whether behavioral and neural alterations of emotional interference and inhibitory control in cPTSD can be improved through 12 months of outpatient treatment with DBT-PTSD

(Bohus et al., 2019) or CPT (Resick et al., 2016). To address this question, we used an adapted version of the Stroop task (see also, Herzog et al., 2019; Thomaes et al., 2012) during fMRI, before and after 12 months of treatment. We used a combined version of cStroop and eStroop, since both were used several times to identify neural dysfunction within regions implicated in emotional interference and inhibitory control in PTSD patients (Bremner et al., 2004), and have been shown to be useful as a measure for treatment outcome in several disorders (Ball et al., 2004; Black et al., 1997; Cooper & Fairburn, 1994; Thomaes et al., 2012). Based on previous studies on Stroop effects in cPTSD after CM (Herzog et al., 2019; Thomaes et al., 2012; Thomaes et al., 2014), and studies on psychotherapy effects on neural processing (Levin et al., 1999; Lindauer et al., 2008; Peres et al., 2011; Peres et al., 2007), we hypothesized that patients after 12 months of treatment will show (a) reduced eStroop interference for trauma-related words, as reflected in faster reaction times and less errors, (b) decreased activation in target limbic brain regions as in the insula and amygdala, and (c) decreased activation in target prefrontal brain regions as in the dACC and dlPFC. Moreover, we aimed to investigate potential treatment-associated behavioral and neural differences between DBT-PTSD vs. CPT as well as correlations between symptom reduction and brain activation within explorative analyses.

4.3 Methods

4.3.1 Participants and Procedure

Patients for the current study were recruited within a large multi-center RCT. The RCT was conducted at 3 sites in Germany (Mannheim, Frankfurt and Berlin), and compared the efficacy of outpatients DBT-PTSD and CPT (German Clinical Trials Registration ID: DRKS00006095) (Bohus et al., 2020). A detailed description of both treatment programs and the study protocol as well as the trial´s results are provided elsewhere (Bohus et al., 2020; Bohus et al., 2019; Dittmann et al., 2017). In short, DBT-PTSD is based on the rules and principles of DBT (Bohus, 2004; Linehan, 1993) and adds interventions derived from trauma-focused CBT, acceptance and commitment therapy, and compassion-focused therapy as well as innovative interventions (Bohus et al., 2019). CPT is an established trauma-focused treatment aiming at challenging dysfunctional trauma-related cognitions and emotions (Resick et al., 2008; Resick et al., 2016). Inclusion criteria for participating in the RCT included female sex and gender identity; an age of 18 to 65 years; a diagnosis of PTSD (according to the DSM-5) following sexual or physical abuse before the age of 18; meeting 3 or more criteria of Borderline Personality Disorder (BPD),

including criterion 6 (affective instability); and availability for 12 months of weekly outpatient treatment. Exclusion criteria for participating in the RCT included lifetime diagnoses of schizophrenia, bipolar I disorder, mental retardation, or severe psychopathology requiring immediate treatment in a different setting (e.g., body mass index <16.5), life-threatening suicide attempts within the last 2 months, current substance dependence (any usage within the last 2 months), medical conditions making exposure-based treatment impossible (e.g., pregnancy), a highly unstable life situation (e.g., homelessness), scheduled residential treatment and receipt of either CPT or DBT-PTSD treatment during the last year. Patients with ongoing self-harm, suicidality, or high-risk behaviors were not excluded. PTSD diagnosis and symptomatology was assessed with the Clinician Administered PTSD Scale for DSM-5 (CAPS-5; Müller-Engelmann et al., 2020; Schnyder, unpublished manuscript, 2013; Weathers et al., 2013), co-occurring disorders with the Structure Clinical Interview for DSM-IV Axis I Disorders (SCID-I; Wittchen et al., 1997). BPD diagnosis was assessed using the BPD section of the International Personality Disorder Examination for the last two years (IPDE; Loranger et al., 1997) and BPD symptoms were assessed using the Zanarini Rating Scale for Borderline Personality Disorder (Zanarini et al., 2003). The time course and severity of CM were assessed using an adapted version of the Maltreatment and Abuse Chronology of Exposure Interview (MACE; Isele et al., 2014; Teicher & Parigger, 2015). All patients received up to 45 weekly psychotherapy sessions over the course of 12 months (high frequency treatment, T1-T5) followed by a booster phase of 3 monthly sessions (T6). Early remission could be achieved by several predefined conditions, all of which had to be fulfilled (i) patient claimed recovery prior to session 45, ii) therapist agreed, iii) supervisor agreed, iv) a blinded rater assessed that the patient no longer met the PTSD diagnosis according to CAPS-5 (Bohus et al., 2020).

For the fMRI study, we only included patients randomized in Mannheim and Frankfurt (due to the long distance from Berlin to Mannheim). Inclusion criteria for the fMRI longitudinal study were participation at fMRI at T1 and completion of 12 months of treatment. Exclusion criteria were metal implants, traumatic brain injuries, left-handedness, and claustrophobia. The fMRI study was approved by the Ethics Board II of Heidelberg University, and the Ethics Board of Frankfurt University, Germany, and was conducted according to the Declaration of Helsinki at the Central Institute of Mental Health in Mannheim. Written informed consent was obtained from the participants after the procedures had been fully explained. All subjects received monetary remuneration for participation in the study. Self-report measures in the fMRI study included retrospective questionnaires on CM (Childhood Trauma Questionnaire; CTQ;

Bernstein & Fink, 1998), PTSD symptomatology (Davidson Trauma Scale; DTS; Davidson et al., 1997), Borderline symptomatology (Borderline Symptom List; BSL-23; Bohus et al., 2001) and severity of depressive symptomatology (Beck Depression Inventory; BDI-II; Hautzinger et al., 2003).

Patients of the current fMRI study underwent fMRI scanning before high frequency treatment at T1 (period of maximum 4 weeks after randomization and beginning of treatment) and after completing high frequency treatment at T5 (period of maximum 4 weeks after high frequency treatment). As opposed to treatment outcomes (Bohus et al., 2020), the observation in the current fMRI study was scheduled at T5, in order to prevent drop out. Of the 193 patients who participated in the RCT main study (Bohus et al., 2020), 130 patients participated in Mannheim and Frankfurt and were eligible for the fMRI study. Of those 130 patients, 56 patients did not meet fMRI inclusion criteria for fMRI study or gave no informed consent to participate. We included 74 patients in the fMRI study at T1. Of those, 48 patients completed 12 months of treatment and 36 gave informed consent to participate in the fMRI study at T5. One dataset had to be excluded due to movement artefacts. Two patients of the current fMRI subsample achieved early remission. However, fMRI scanning was conducted at T5 (after 12 months) to achieve comparable conditions. Of these resulting 35 patients, 18 had received DBT-PTSD, and 17 had received CPT. For a detailed patient flow of the current fMRI study, see Figure 4.1.

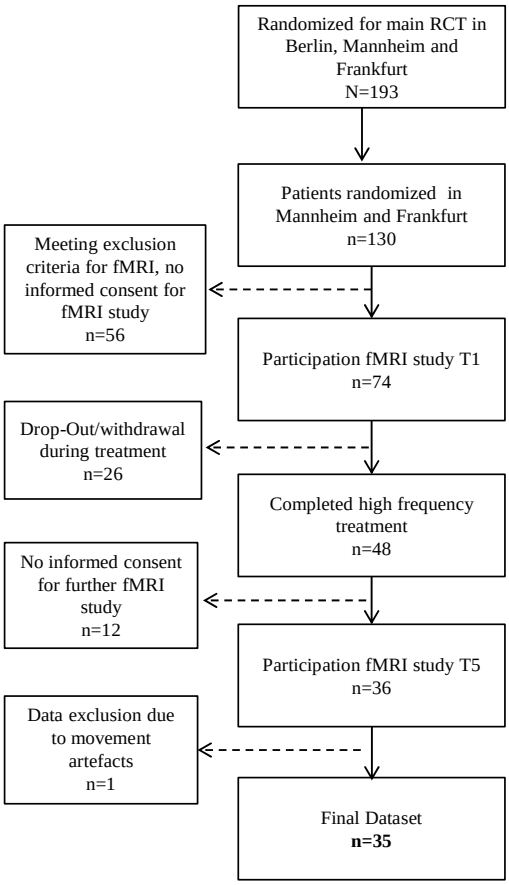


Figure 4.1 Flowchart detailing the selection of the patients for this study. RCT=Randomized controlled trial. For detailed information regarding patient flow in the main RCT, see (Bohus et al., 2020)

4.3.2 Stroop Task

The Stroop Task used here was an adapted version combining both the cStroop and eStroop in one paradigm (see also, Herzog et al., 2019; Thomaes et al., 2012). The paradigm encompassed four different word categories (trauma-related, negative, neutral, color) that were presented in 80 randomized blocks of four words each (20 blocks for each word category). Within the blocks, we included 20 trauma-related words (e.g., *ABUSE*), 20 general negative words (e.g., *CRY*), 20 neutral words (e.g., *SHAPE*) to assess emotional Stroop effects. Furthermore, we used four color words in congruent (e.g., *RED* written in red), as well as incongruent conditions (e.g., *RED* written in blue) to assess classical Stroop effects. Neutral words were used as baseline condition. The process of the word selection for the EST can be found in (Herzog et al., 2019). Each word was presented for 1500 ms, and inter-stimulus intervals between words were jittered with a mean of 300 ms. Inter-trial intervals (i.e., a fixation cross) between task blocks were optimized with optseq2 (http://surfer.nmr.mgh.harvard.edu/optseq), with a mean of 798.77 ms. Before scanning, color naming was practiced in 20 trials with non-word stimuli (e.g., *XXX*

written in red). After the scanning session, participants rated all words regarding valence and arousal on a five point Likert scale by the self-assessment manikin scale (SAM; Bradley & Lang, 1994).

4.3.3 MRI acquisition and data pre-processing

Scanning was conducted on a Siemens 3 Tesla TRIO-Scanner (Siemens Medical Solutions, Erlangen, Germany), using three-dimensional magnetization-prepared rapid-acquisition gradient echo (MPRAGE; T1-weighted contrast, voxel size 1x1x1 mm^3), and an gradient- echo-planar sequence sensitive to the BOLD contrast for functional images (EPI, T2-weighted contrast, 36 transversal slices 3 mm descending, field of view 192x192 mm, voxel size 3x3x3 mm^3, 64x64 voxel matrix, flip angle 80°, echo time 30 ms, repetition time 2000 ms). The first five scans were discarded to minimize T1 effects. Head movement artefacts and scanning noise were restricted using head cushions and headphones.

4.3.4 Statistical Analyses

4.3.4.1 Clinical and Behavioral Data

Clinical measures (CAPS-5, BDI-II, DTS) and demographic data were compared between T1 and T5 (within both treatment groups) using paired sample *t*-tests. Since the current longitudinal fMRI subsample was very selective (i.e., meeting fMRI inclusion criteria at T1, completion of 12 months of treatment, participating at fMRI at T1 and T5), we compared the longitudinal fMRI subsample (n=35) with those who did not meet inclusion criteria for the longitudinal fMRI study (i.e., no participation at fMRI at T1, treatment drop-outs, no informed consent to participate at T5) (N=95) regarding main demographic and clinical variables at T1. Reaction times (RTs; in ms) were log-transformed (base10) to obtain distributions that are in line with the assumption of normality (Ratcliff, 1993). Task performance, i.e., accuracy and RTs was analyzed via repeated measures analysis of variance (rmANOVA), including the within-subject factor 'condition' (difference scores: negative minus neutral vs. trauma minus neutral vs. color minus neutral) and the within-subject factor 'time' (T1 vs. T5). In case of significant effects, post-hoc Bonferroni-corrected *t*-tests and effect sizes (partial eta-squared [η^2_p], Cohen's *d* [40]) were computed. All analyses were performed with IBM SPSS Statistics 25 (IBM, USA), assuming a statistical significance level of $p<.05$, using Greenhouse-Geisser correction when

necessary. For explorative analyses, treatment condition was included as an additional factor, and change in PTSD symptoms was correlated to changes in brain activation.

4.3.4.2 fMRI Data

Functional imaging data were analyzed using standard procedures implemented in Statistical Parametric Mapping (SPM 8; Welcome Department of Cognitive Neurology, London, UK; www.fil.ion.ucl.ac.uk/spm/). EPI time series were pre-processed according to custom practice, including slice time correction, spatial realignment, segmentation of T1 scan, co-registration onto T1 scan, normalization to the standard brain of the Montreal Neurological Institute (MNI) space, smoothing with a Gaussian kernel with a full-width at half maximum of 6mm. One participant had to be excluded due to excessive head motion (more than 3mm). First-level analyses were set up as word blocks with negative, trauma, neutral, and color (cStroop) words as regressors of interest, as well as regressors of no interest, modelling button presses and movement parameters as. We defined the following differential contrasts at the subject level: i) negative>neutral, ii) trauma>neutral, and iii) color>neutral. For whole-brain analyses, a full factorial model (two time points x three conditions) was used including the *F* contrast 'main effect of time' (T1 and T5), 'main effect of condition' (negative>neutral, trauma>neutral and color>neutral) and interaction effect 'time by condition'. In line with the literature of treatment effects in PTSD and according to our hypotheses, we specifically hypothesized treatment effects during the processing of trauma-related stimuli in the amygdala, insula, dlPFC and dACC. Accordingly, we used anatomical masks (left and right hemisphere separately), as defined by the Automated Anatomical Labeling software (Tzourio-Mazoyer et al., 2002). For main and interaction effects, family-wise error (FWE) correction for multiple comparisons was conducted at the whole-brain level ($p_{FWE}<.05$), and also for each ROI (small volume corrected, SVC), based on an initial cluster-forming threshold of $p<.001$. For the ROI analyses, we additionally corrected for multiple comparisons of the 8 ROIs (amygdala, insula, dlPFC and dACC for each hemisphere) with a Bonferroni correction, yielding p_{-FWE} -values of <.00625 (i.e., 0.05/8) indicating statistical significance. In case of significant differences, two-tailed post-hoc Bonferroni-corrected *t*-tests ($p<.05$) were performed after extracting beta values of the respective peak voxel using SPSS, and effect sizes (η^2_p, Cohen's *d*) were computed.

4.3.4.3 Exploratory Analyses

To investigate the association of treatment effects with behavioral performance, we further conducted correlation analyses between changes in behavioral task performance from T1 to T5 (Δ reaction times and Δ correct reactions) with changes on symptom severity (Δ CAPS-5) using Pearson correlations. To investigate the association between treatment effects and alterations in brain activation, we further conducted correlation analyses between changes in extracted beta values of the respective peak voxel from T1 to T5 (Δ brain activation) and changes in symptom severity (Δ CAPS-5) using Pearson correlations, independent of treatment groups. For exploratory analyses regarding differences between treatment groups, all analyses were repeated with the additional factor 'treatment group' (DBT-PTSD vs. CPT).

4.4 Results

4.4.1 Clinical and Behavioral Results

Details on clinical measures, demographic data and behavioral performance of the current sample (n=35) as well as treatment effects on all variables are reported in Table 4.1. CAPS-5 total severity, DTS, BDI-II, BSL-23 and ZAN scores significantly improved from T1 to T5 (Table 4.1). The use of psychotropic medication did not change significantly. Patients of the current longitudinal study (n=53) did not differ significantly from those patients who were not included in the current study (n=95) on demographic and clinical variables at T1, see Table 4.4. For interference scores regarding RTs and accuracy, we found a significant main effect for condition (RT: $F_{2,68}$=7.09, p<.01, η^2_p=0.17; accuracy: $F_{2,68}$=3.13, p<.05, η^2_p=0.08), a significant main effect for time (RT: $F_{1,34}$=10.35, p<.01, η^2_p=0.23; accuracy: n.s.) as well as a significant interaction between time and condition (RT: $F_{2,68}$=6.22, p<.01, η^2_p=0.16; accuracy: $F_{2,68}$=3.86, p<.05, η^2_p=0.10) (Table 4.2). Regarding the interaction effect of interest (time by condition), post-hoc comparisons between T1 and T5 revealed that Stroop interference significantly decreased for the trauma condition, with faster RTs ($t_{(34)}$=4.07, p<.001, d=0.69) and less errors ($t_{(34)}$=2.11, p<.05, d=0.57) (Figure 4.2). Results of post-hoc t-tests for the negative and color conditions were not significant, see Table 4.2.

Table 4.1 Descriptive and clinical data as well as treatment effects in patients with complex posttraumatic stress disorder

	Patients (n = 35)				Test of treatment effects		
Demographics	T1		T5		Test value (df)	p (two-tailed)	
	M	(SD)	M	(SD)			
Age	36.89[a]	(12.51)	-			-	
Years of education	10.34[a]	(1.35)	-			-	
Clinical Characteristics	M	(SD)					
CTQ - total score (SD)	77.74	(22.93)	-			-	
DTS - total score (SD)	74.70	(18.76)	35.06	(28..83)	$t_{(30)}$=8.13	<.001	T1>T5
BDI II - total score (SD)	36.14	(9.54)	17.45	(14.39)	$t_{(32)}$=7.41	<.001	T1>T5
CAPS 5 - total score (SD)	41.14	(9.93)	20.15	(14.93)	$t_{(33)}$=8.22	<.001	T1>T5
BSL-23 - mean score (SD)	1.89	(0.75)	1.01	(0.79)	$t_{(34)}$=6.1	<.001	T1>T5
ZAN - total score (SD)	9.83	(5.39)	4.66	(4.63)	$t_{(34)}$=5.81	<.001	T1>T5
Current Comorbidities	N	(%)					
Affective Disorders	25	(71.4)	9	(25.7)	$\chi^2_{(1)}$=14.64	<.001	T1>T5
Anxiety Disorders	21	(60.0)	12	(34.3)	$\chi^2_{(1)}$=4.64	<.05	T1>T5
Substance Dependency/Abuse Disorders	0	-	0	-		-	
Obsessive Compulsive Disorders	4	(11.4)	3	(8.6)	$\chi^2_{(1)}$=0.16	.69	n.s.
Somatization Disorders	2	(5.7)	2	(5.7)	$\chi^2_{(1)}$=0.00	1	n.s.
Eating Disorders	5	(14.3)	2	(5.7)	$\chi^2_{(1)}$=1.43	.23	n.s.
Psychotropic Medication	N	(%)					
SSRI	9	(25.7)	7	(20)	$\chi^2_{(1)}$=0.32	.57	n.s.
SNRI	8	(22.9)	7	(20)	$\chi^2_{(1)}$=0.09	.77	n.s.
Other Antidepressants	9	(25.7)	8	(22.9)	$\chi^2_{(1)}$=0.32	.57	n.s.
Neuroleptics	8	(22.9)	5	(14.3)	$\chi^2_{(1)}$=0.85	.36	n.s.
Sedatives/Anxiolytics		-				-	
Mood Stabilizers	2	(5.7)	2	(5.7)	$\chi^2_{(1)}$=0.00	1	n.s.
Reaction Times in ms	M	(SD)					
Negative words	800.82	(177.17)	779.49	154.77	$t_{(34)}$=1.64	0.11	n.s.
Trauma words	868.29	(206.40)	797.47	165.32	$t_{(34)}$=3.49	<.001	T1>T5
Neutral words	781.71	(170.18)	770.27	145.63	$t_{(34)}$=0.68	0.50	n.s.
Color words	855.72	(181.49)	826.17	161.61	$t_{(34)}$=1.72	0.10	n.s.
Accuracy in % correct responses	%	(SD)					
Negative words	93.43	(15.13)	93.82	(13.90)	$t_{(34)}$=1.35	0.19	n.s.
Trauma words	91.36	(16.46)	97.14	(5.48)	$t_{(34)}$=2.28	<.05	T1<T5
Neutral words	94.86	(11.36)	95.92	(10.03)	$t_{(34)}$=1.26	0.22	n.s.
Color words	89.36	(16.73)	91.28	(13.68)	$t_{(34)}$=1.65	0.11	n.s.

Note. CTQ = Childhood Trauma Questionnaire; DTS = Davidson Trauma Scale, BDI-II = Beck Depression Inventory II, CAPS-5 = Clinician Administered PTSD Scale for DSM-5, BSL-23 = Borderline Symptom List 23, ZAN = Zanarini Rating Scale for Borderline Personality Disorder, M = mean; SD = standard deviation; ms = milliseconds; n.s.= not significant at a significance level of p<.05; [a]Participants age and education at T1.

Table 4.2 Behavioral data of Stroop interference scores in patients with complex posttraumatic stress disorder

	Patients (n = 35)				Test of treatment effects			
Reaction Times in ms[a]	T1		T5		*Test value (df)*	*p (two-tailed)*	*Cohens' d*	
	M	(SD)	M	(SD)				
Negative>neutral words	0.01	(0.02)	0.00	(0.03)	$t_{(34)}$=1.21	.24	0.23	n.s.
Trauma>neutral words	0.04	(0.05)	0.01	(0.04)	$t_{(34)}$=4.07	<.001	0.69	T1>T5
Color> neutral words	0.04	(0.05)	0.03	(0.05)	$t_{(34)}$=1.49	.15	0.2	n.s.
Accuracy in % correct responses	%	(SD)	%	(SD)				
Negative>neutral words	-0.01	(0.06)	-0.02	(0.10)	$t_{(34)}$=0.98	.34	0.09	n.s.
Trauma>neutral words	-0.04	(0.08)	0.01	(0.08)	$t_{(34)}$=2.11	<.05	0.57	T1<T5
Color> neutral words	-0.06	(0.10)	-0.05	(0.09)	$t_{(34)}$=0.71	.48	0.09	n.s.

Note. cPTSD = Complex Posttraumatic Stress Disorder; M = mean; SD = standard deviation; n.s.= not significant at a significance level of p<.05; [a]Reaction times were log-transformed for analyses and refer to correct responses.

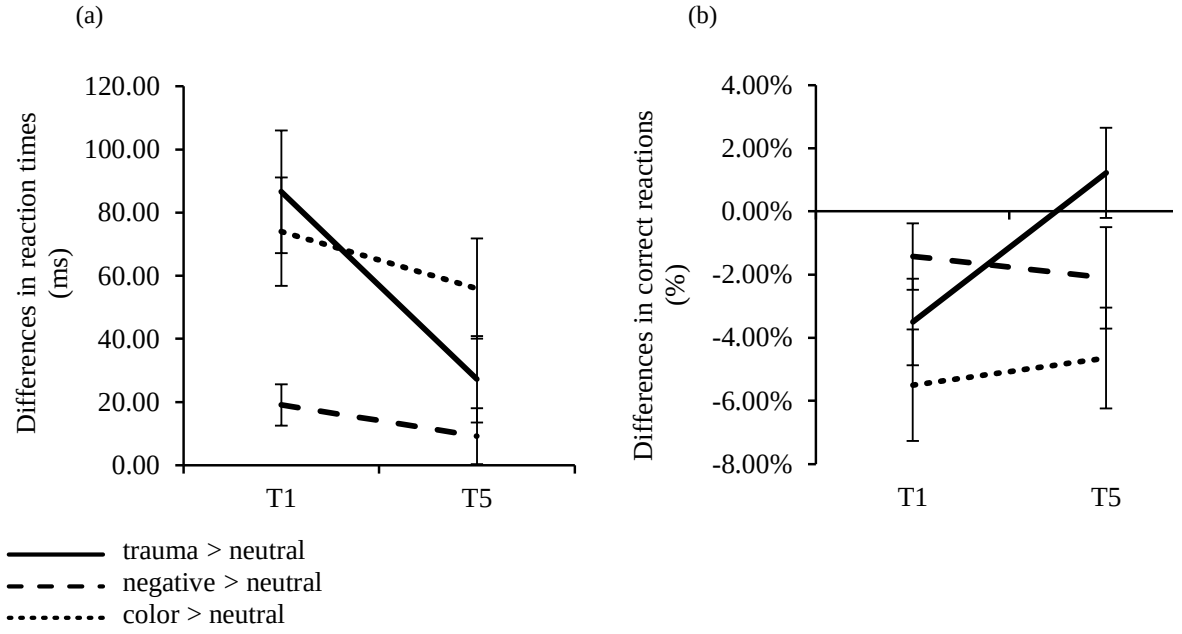


Figure 4.2 Means ± standard error of the mean (SEM) at T1 and T5 of interference scores of reaction times (ms) (Figure 1a) and correct reactions (%) (Figure 1b) in patients with complex posttraumatic stress disorder (cPTSD). T1=before high frequency treatment. T5=after high frequency treatment. Lines and asterisks above bars on bar graph indicate significant differences of post-hoc *t*-tests amongst time during the experimental conditions. *** p< .001, ** p<.01, * p<.05, ^{+}p<.09

4.4.2 FMRI Results

At whole brain level, we observed clusters that survived FWE-correction for the *F* contrast condition, in the inferior parietal lobule and the middle temporal gyrus among others. We did not observe any clusters that survived FWE-correction for the *F* contrast time and the interaction time by condition. For complete description of suprathreshold clusters of the main effect of condition, main effect of time, and interaction effect of time by condition, see Table 4.5. Small-volume corrected analyses for the hypothesized regions of interest, corrected for multiple comparisons, revealed a significant interaction (time by condition) for the left amygdala (MNI, *x,y,z*=-33,2,-20, k_E=13, $F_{(1.52,51.61)}$=12.03, $p_{SVC\text{-}FWE}$<.001, η^2_p=0.26), the right anterior insula (MNI, *x,y,z*=30,26,13 k_E=50, $F_{(2,68)}$=11.94, $p_{SVC\text{-}FWE}$<.001, η^2_p=0.25), the right dlPFC (MNI, *x,y,z*=45,8,37, k_E=102, $F_{(1.70,57.95)}$=7.93, $p_{SVC\text{-}FWE}$=.001, η^2_p=0.19) and the right dACC (MNI, *x,y,z*=12,44,7, k_E=33, $F_{(1.51,51.30)}$=12.34, $p_{SVC\text{-}FWE}$<.001, η^2_p=0.27). Post-hoc *t*-tests revealed significant differences with large effect sizes from T1 to T5 for the trauma condition in all clusters (amygdala: $t_{(34)}$=3.32, *p*<.001, *d*=0.74; insula: $t_{(34)}$=3.75, *p*<.001, *d*=0.88; dlPFC: $t_{(34)}$=3.49, *p*<.001, *d*=0.67; dACC: $t_{(34)}$=2.73, *p*<.01, *d*=0.70), indicating a decrease in brain activation during the processing of trauma-related words over time (Figure 4.3 a-d). Results of post-hoc *t*-tests for the negative and color condition showed no significant alterations from T1 to T5, see Table 4.3.

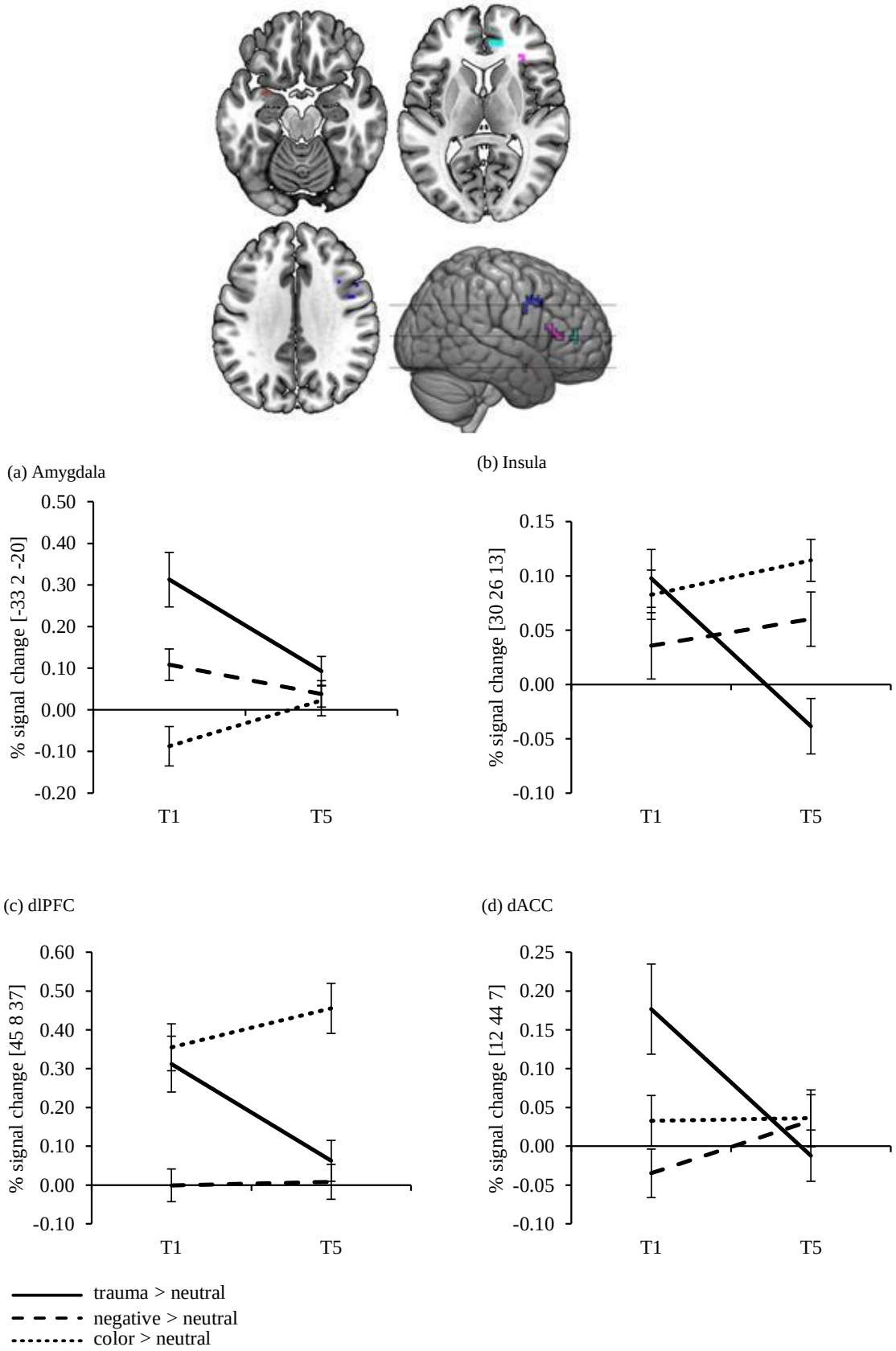


Figure 4.3 Significant clusters in the condition by time interaction for (a) the amygdala [-33, 2, -20; red blobs], (b) insula [30, 26, 13; violet blobs], (c) dorsolateral prefrontal cortex (DLPFC) [45, 8, 37; blue blobs], and (d) dorsal anterior cingulate cortex (dACC) [12, 44, 7; cyan blobs] at T1 and T5 in patients with complex

posttraumatic stress disorder (cPTSD). T1=before high frequency treatment. T5=after high frequency treatment. For illustration purposes, the statistical threshold was set to p<.01, uncorrected. Error bars represent standard error of the mean (SEM). Lines and asterisks above bars on bar graph indicate significant differences of post-hoc t-tests amongst groups during the experimental conditions. *** $p < .001$, ** $p<.01$, * $p<.05$

Table 4.3 Results of the post-hoc *t*-tests based on the region of interest analyses of the stroop task in patients with complex posttraumatic stress disorder

		Patients (n = 35)				Test of treatment effects			
Region of Interest	Contrast	T1		T5		*Test value (df)*	*p (two-tailed)*	*Cohens' d*	
		M	(SD)	M	(SD)				
Left Amygdala [MNI: -33, 2, -20]	Neg>neu	0.19	(0.22)	0.04	(0.19)	$t_{(34)}$=1.40	.17	0.34	n.s.
	Tra>neu	0.31	(0.39)	0.09	(0.21)	$t_{(34)}$=3.32	<.001	0.74	T1>T5
	Col> neu	-0.09	(0.28)	0.02	(0.22)	$t_{(34)}$=-1.66	.12	0.44	n.s.
Right Insula [MNI: 30, 26, 13]	Neg>neu	0.04	(0.18)	0.06	(0.15)	$t_{(34)}$=-0.65	.52	0.15	n.s.
	Tra>neu	0.10	(0.16)	-0.04	(0.15)	$t_{(34)}$=3.75	<.001	0.88	T1>T5
	Col> neu	0.08	(0.13)	0.11	(0.11)	$t_{(34)}$=-1.18	.25	0.25	n.s.
Right dlPFC [MNI: 45, 8, 37]	Neg>neu	0.01	(0.25)	0.01	(0.27)	$t_{(34)}$=-0.16	.88	0.03	n.s.
	Tra>neu	0.31	(0.43)	0.06	(0.31)	$t_{(34)}$=3.49	<.001	0.67	T1>T5
	Col> neu	0.36	(0.35)	0.46	(0.38)	$t_{(34)}$=-1.06	.23	0.27	n.s.
Right dACC [MNI: 12, 44, 7]	Neg>neu	-0.03	(0.19)	0.03	(0.20)	$t_{(34)}$=-1.42	.15	0.35	n.s.
	Tra>neu	0.18	(0.34)	-0.01	(0.19)	$t_{(34)}$=2.73	<.01	0.7	T1>T5
	Col> neu	0.03	(0.19)	0.09	(0.21)	$t_{(34)}$=-1.52	.14	0.3	n.s.

Note. cPTSD = Complex Posttraumatic Stress Disorder; M = mean; SD = standard deviation; dlPFC = dorsolateral prefrontal cortex; dACC = dorsal anterior cingulate cortex; neg=negative words, tra=trauma words, col=color words, MNI = Montreal Neurological Institute; n.s.= not significant at a significance level of $p<.05$.

4.4.3 Exploratory Results

We found no significant correlations of symptom improvement (Δ CAPS-5) with changes in Stroop performance (Δ reaction times, Δ correct reactions), or changes in brain activation (Δ brain activation in all of four clusters) (Table 4.6). With regard to differential treatment group effects (DBT-PTSD vs. CPT), no significant differences were found between the treatment groups for any of the demographic or clinical variables at T1 and T5. From T1 to T5, patients in both treatment groups significantly improved on all clinical variables (Table 4.7). Moreover, we found no significant effects for treatment group on behavioral or neural measures (Table 4.8) in our sub-sample. Moreover, we found no significant correlations of symptom improvement (Δ CAPS-5) with changes in Stroop performance (Δ reaction times, Δ correct

reactions), nor with brain activation (Δ brain activation in all of four clusters), when investigating both treatment groups separately (Table 4.9).

4.5 Discussion

The goal of this study was to examine whether behavioral and neural measures of emotional interference and inhibitory control in cPTSD after CM can be altered by 12 months of outpatient treatment with DBT-PTSD or CPT. In line with our hypothesis, after 12 months of treatment, patients exhibited faster reaction times and less errors, thereby supporting Hypothesis a. At the brain level, we found decreased activation in the amygdala and insula (supporting Hypothesis b), and decreased activation in the dlPFC and dACC (supporting Hypothesis c) during the processing of trauma-related words compared to neutral and negative words and compared to pretreatment. With regard to hypotheses a and b, our results are in line with previous treatment studies in adult-trauma PTSD patients, which revealed improved performance during the processing of emotional stimuli in various paradigms as well as decreased activation in the amygdala and insula after psychotherapy (Aupperle et al., 2013; Fonzo et al., 2017b; Peres et al., 2007; Roy et al., 2014; Roy et al., 2010). The amygdala plays a key-role in threat and fear processing, so that one can assume that decreased activation may be a correlate of reduced reactivity in response to (threatening) trauma-related stimuli associated with treatment. The repeated adaption of new information regarding traumatic memories in both treatments may have promoted corrective learning towards the discrimination of safety from threat and habituation towards traumatic stimuli. This strategy may have resulted in reduced fear processing represented by decreased amygdala responsivity (Foa & Kozak, 1986; Fonzo et al., 2017b). In the same vein, the insular cortex is supposed to play a role in anxiety processing in general, but can be functionally divided into anterior and posterior parts. Parts of the anterior insula have found to be related to the detection of salient stimuli and are assumed to be important for effective modulation of attention in the presence of emotional stimuli (Smith et al., 2014), whereas posterior parts are more linked to the representation of interoceptive and bodily state changes. Hence, decreased activation in the anterior insula may be interpreted as a correlate of reduced alertness and hyperarousal in the context of trauma-related stimuli. This could be related to therapeutic interventions that strengthen inhibitory control and modulate attention as used in both, DBT-PTSD and CPT. Moreover, we found decreased activation in the dACC and dlPFC following 12 months of treatment (Hypothesis c). These results are not in line with numerous studies in adult-trauma related PTSD, demonstrating increased dACC and

dlPFC (but see, Franklin et al., 2015; Kane & Engle, 2002) activation together with decreased limbic activation posttreatment, which have been discussed to reflect regained prefrontal inhibitory control over previously limbic hyperactivation (Malejko et al., 2017; Thomaes et al., 2014; Yang et al., 2018). However, our results are in line with a recent study that assessed neural correlates of emotion processing and regulation in military veterans with and without PTSD before and after treatment with/without PE and medication. After treatment, participants showed less recruitment of prefrontal regions during reappraisal of negative emotions (Joshi et al., 2020). Using a similar paradigm as in the current study, others also found decreased dlPFC, dACC and insula activation following treatment (Thomaes et al., 2012).

A recent review highlighted the role of the amygdala and dACC, together with insula as important nodes in the salience and threat detection system, suggesting that alterations within this system may contribute to PTSD psychopathology (Sheynin & Liberzon, 2017). Moreover, the dlPFC region has (next to other PFC regions) repeatedly been found to be implicated in emotion regulation capacity in order to restructure cognitions or memories in reaction to perceived threat (Aupperle et al., 2013; Lindauer et al., 2008; Marwood et al., 2018; Thomaes et al., 2014) and has demonstrated greater activation in participants with PTSD undergoing emotion regulation tasks (Buhle et al., 2014). In this vein, the current findings of reduced emotional reactivity on the behavioral level, accompanied by reduced amygdala, insula, dACC activation and dlPFC activation might suggest that decreased emotional reactivity may have contributed to a decreased need for prefrontal regulation within the dlPFC (Joshi et al., 2020). In other words, one may tentatively conclude that decreased emotional interference in cPTSD patients during the Stroop task may have resulted in lower demands in prefrontal activation to compensate for interference, leading to decreased and *normalized* activation, and regained capacity to respond appropriately when necessary (Joshi et al., 2020; Marwood et al., 2018).

With regard to exploratory analyses, we found no treatment-associated neural or behavioral differences. Although DBT-PTSD was found superior in treating cPTSD patients in the intent-to-treat sample of the main RCT (Bohus et al., 2020), both treatments significantly improved clinical measures in our sub-sample, which is consistent with previous studies demonstrating the effectiveness of both treatments in cPTSD related to CM (Bohus et al., 2013; Granato et al., 2015; Resick et al., 2008). This might be interpreted in terms that both treatments, albeit using different techniques, aim to reduce trauma-associated responses by working with trauma-related memories, cognitions, and emotions. These techniques may have led to habituation regarding trauma- related stimuli, as reflected in decreased emotional interference during the

Stroop task, following both types of intervention. Apart from several strengths of our study, as this study represents one of the largest fMRI treatment studies in PTSD patients in general, and particularly in CM-related cPTSD, we also have to point out several limitations. First, our statistics are limited by low statistical power due to participant dropout, and therefore our results were at risk for false negative results to reliably assess correlations between symptom improvement, behavioral and neural measures and might therefore have caused false negative results. With the given sample size of n=35, α=.05 and β=.05, a sensitivity power analysis conducted with G*Power (Faul et al., 2007) indicated that the smallest correlation that can be detected is a correlation ρ=0.52. This means that we cannot rule out correlations smaller than ρ=0.4 with sufficient certainty, given the sample size. Since small correlations are plausible yet, future studies with larger sample sizes are needed. Therefore, future treatment studies should recruit larger sample sizes before treatment, try to minimize treatment drop-outs or try to offer better incentives for patients to participate in a follow-up fMRI session. We were further underpowered to detect differences in neural function between the both treatments. Thus, we are not able to determine whether different treatments (DBT-PTSD or CPT) impact neural and behavioral functions differently. Since we included no waiting group, we cannot rule out the possibility that changes after 12 months of treatment were due to natural recovery processes, or effects of repeated testing/habituation, rather than treatment. Future research using randomized designs with waiting groups in conjunction with neuroimaging is needed to further delineate mechanisms of changes that are attributable to treatment. Since our study was part of a larger RCT, we had to include patients with comorbid disorders and psychotropic medication. However, it has to be noticed that cPTSD related to CM is associated with a high frequency of co-occurring disorders, such as depression, anxiety and personality disorders (Brewin, 2019; Cloitre et al., 2013; Green et al., 2010). Therefore, our sample is in this aspect representative for this group of patients.

It is important to note, that we were not able to use the official diagnostic criteria of cPTSD as defined by the ICD-11 (World Health Organization, 2018). Unfortunately, official diagnostic criteria of cPTSD were not available when our study started. Therefore, we defined inclusion criteria for the study (i.e., diagnosis of PTSD following repeated sexual or physical abuse before the age of 18 and meeting 3 or more criteria of BPD, including the criterion for affective instability) that they best reflect the clinical profile of cPTSD (Brewin et al., 2017; Cloitre et al., 2013). Furthermore, we cannot rule out that medication had an impact on our results. However, the percentage of medicated patients was comparable in both treatment arms, and

medication did not significantly differ between fMRI measurements. To clarify the impact of medication and comorbidity, it would be useful to further explore medication and comorbidity interaction with emotion processing, neural correlates and treatment effects in larger PTSD subpopulations with or without medication and with or without comorbidities in future large-scale studies.

To conclude, as one of the largest treatment studies in CM-related cPTSD patients, our study shows that pathologically increased emotional interference by trauma-related cues decreased after 12 months of psychotherapeutic treatment, as reflected in behavioral and neural measures. This might point to a *normalization* of the cPTSD-related neural patterns, possibly by integrating new adaptive information to distinguish between threat and safety, resulting in lower emotional interference and limbic activation, and consequently a decreased need of compensatory prefrontal activation to face trauma-related cues.

4.6 Supplementary Material

Table 4.4 Demographic and clinical variables at T1 of patients participated in the fMRI longitudinal study vs. those who did not participate

	Patients participated in the current study (n = 35)		Patients who did not participate in the current study (n = 95)		Group differences T1		
Demographics	T1		T1		*Test value (df)*	*p (two-tailed)*	
	M	(SD)	M	(SD)			
age mean	36.89	(12.51)	36.57	(10.99)	$t_{(128)}$=0.14	.89	n.s
years of education	10.34	(1.35)	10.65	(1.32)	$t_{(128)}$=1.18	.24	n.s
Clinical characteristics	M	(SD)	M	(SD)			
CTQ - total score	77.74	(22.93)	76.78	(19.76)	$t_{(126)}$=0.23	.86	n.s
DTS - total score	74.70	(18.76)	77.03	(20.96)	$t_{(123)}$=0.56	.57	n.s
BDI II - total score	36.14	(9.54)	32.51	(12.43)	$t_{(128)}$=1.57	.12	n.s
CAPS 5 - total score	41.14	(9.93)	42.38	(10.13)	$t_{(128)}$=0.62	.53	n.s
BSL-23 - mean score	1.89	(0.75)	1.95	(0.85)	$t_{(128)}$=0.39	.70	n.s
ZAN - total score	9.83	(5.39)	9.97	(4.91)	$t_{(126)}$=0.14	.89	n.s

Note. CTQ = Childhood Trauma Questionnaire; DTS = Davidson Trauma Scale, BDI-II = Beck Depression Inventory II, CAPS-5 = Clinician Administered PTSD Scale for DSM-5, BSL-23 = Borderline Symptom List 23, ZAN = Zanarini Rating Scale for Borderline Personality Disorder, M = mean; SD = standard deviation; n.s.= not significant at a significance level of $p<.05$.

Table 4.5 Activated brain areas (BOLD responses with peak MNI coordinates) in patients with complex posttraumatic stress disorder during the Stroop task

F contrast	Anatomical label	BA	Cluster size	Peak voxel (MNI)			Voxel Z	p_{FWE}	*P* *(uncorrected)*
				x	y	z			
Main effect 'condition'	Cuneus	BA 17	17506	-9	-88	4	6.55	<.001	<.001
	Cuneus	BA 17		9	-85	4	6.55	<.001	<.001
	Inferior Parietal Lobule	BA 40		-48	-43	52	6.55	<.001	<.001
	Middle Temporal Gyrus	BA 21	47	63	-4	-11	4.52	0.09	<.001
	Middle Temporal Gyrus	BA 21		48	-1	-20	3.90	0.62	<.001
	Precentral Gyrus	BA 4	13	39	-28	67	4.43	0.12	<.001
	Anterior Lobe	*	48	0	-58	-35	4.37	0.15	<.001
	Precentral Gyrus	BA 6	76	57	-4	7	4.33	0.18	<.001
	Insula	BA 13		39	-19	19	4.18	0.29	<.001
	Insula	BA 13		45	-10	13	3.66	0.88	<.001
	Superior Temporal Gyrus	BA 38	22	42	23	-32	4.02	0.47	<.001
Main effect 'time'		*	49	27	23	19	4.21	0.25	<.001
Interaction effect 'time by condition'	Anterior Cingulate	BA 32	12	12	44	7	4.09	0.39	<.001
	Middle Frontal Gyrus	BA 6	10	-24	-4	40	4.01	0.48	<.001
	Superior Temporal Gyrus	BA 38	19	57	32	10	3.81	0.73	<.001
	Sub-lobar	*		60	23	7	3.49	0.97	<.001
	Inferior Frontal Gyrus	BA 46	43	60	-40	34	3.78	0.76	<.001
	Inferior Frontal Gyrus	BA 45		69	-28	19	3.67	0.87	<.001
	Inferior Parietal Lobule	BA 40		48	-40	34	3.55	0.95	<.001
	Postcentral Gyrus	BA 40	17	51	17	-20	3.74	0.81	<.001
	Inferior Parietal Lobule	BA 40		48	11	-26	3.43	0.99	<.001
	Sub-lobar	Caudate Body	17	45	-4	37	3.68	0.87	<.001
	Superior Temporal Gyrus	BA 38		45	8	37	3.62	0.91	<.001
	Superior Temporal Gyrus	BA 38	14	21	-100	4	3.66	0.88	<.001
	Sub-lobar	Medial Globus Pallidus		12	-100	7	3.60	0.93	<.001
	Cingulate Gyrus	BA 24	11	-6	-4	73	3.57	0.94	<.001

Note. BOLD = Blood oxygenation level-dependent; MNI = Montreal Neurological Institute; BA= Brodmann area; FWE = family-wise error corrected.

Table 4.6 Correlations between changes on CAPS-5 symptom severity (Δ CAPS-5) with changes in Stroop performance (Δ reaction times, Δ correct reactions) and brain activation (Δ brain activation in all of four clusters) from T1 to T5 in patients with complex posttraumatic stress disorder

		Δ Reaction Times [a]			Δ Correct Reactions			Δ Amygdala activation			Δ Insula activation			Δ dlPFC activation			Δ dACC activation		
n=35		neg> neu	tra> neu	col> neu	neg> neu	tra> neu	col> neu	neg> neu	tra> neu	col> neu	neg> neu	tra> neu	col> neu	neg> neu	tra> neu	col> neu	neg> neu	tra> neu	col>neu
Δ CAPS-5	Pearson Correlation	0.14	0.12	0.05	0.04	-0.10	-0.06	0.06	0.23	0.09	0.16	0.20	0.16	0.01	0.18	0.06	0.08	0.24	-0.22
	Sig. (2-tailed)	0.41	0.47	0.78	0.81	0.55	0.72	0.73	0.19	0.57	0.35	0.23	0.34	0.97	0.30	0.75	0.65	0.15	0.18

Note. [a]Reaction times were log-transformed for analyses and refer to correct responses; neg=negative words, tra=trauma words, col=color words; dlPFC=dorsolateral prefrontal cortex, dACC=dorsolateral prefrontal cortex.

Table 4.7 Demographic and clinical variables and treatment effects in patients with complex posttraumatic stress disorder undergoing Dialectical Behavioral Therapy for PTSD and Cognitive Processing Therapy

	DBT-PTSD patients (n = 18)				CPT patients (n = 17)				Group differences T1			Test of treatment effects[b]		
	T1		T5		T1		T5		Test value (df)	p (two-tailed)		Test value (df)	p (two-tailed)	
Demographics	M	(SD)	M	(SD)	M	(SD)	M	(SD)						
age mean	37.11[a]	(11.88)		-	36.65[a]	(13.50)		-	$t_{(33)}$=0.11	.92	n.s	-		
years of education	10.17[a]	(1.47)		-	10.53[a]	(1.23)		-	$t_{(33)}$=0.79	.44	n.s	-		
Clinical Characteristics														
CTQ - total score	82.39	(15.77)	-		72.82	28.34	-	-	$t_{(33)}$=1.24	.22	n.s	-		
DTS - total score	73.82	(16.48)	33.18	(31.12)	75.53	(21.01)	37.07	(27.06)	$t_{(31)}$=0.26	.8	n.s	$F_{(1,29)}$= 0.03	.86	n.s.
BDI II - total score	38,11	(9.00)	16,47	(15.77)	34,06	(9.92)	18,50	(13.21)	$t_{(33)}$=1.27	.21	n.s	$F_{(1,33)}$= 1.45	.24	n.s.
CAPS 5 - total score	42.39	(10.16)	20.35	(18.06)	39.82	(9.81)	19.94	(11.56)	$t_{(33)}$=0.76	.45	n.s	$F_{(1,33)}$= 0.22	.65	n.s.
BSL23 - mean score	1.99	(0.69)	0.93	(0.85)	1.77	(0.81)	1.02	(0.75)	$t_{(33)}$=0.86	.38	n.s	$F_{(1,33)}$= 1.02	.32	n.s.
ZAN - total score	10.72	(5.14)	4.89	(5.51)	8.88	(5.64)	4.41	(3.64)	$t_{(33)}$=1.0	.32	n.s	$F_{(1,33)}$= 0.58	.45	n.s.
Current Comorbidities	N	(%)	N	(%)	N	(%)	N	(%)						
Affective Disorders	15	(83.3)	6	(33.3)	10	(58.8.)	3	(17.6)	$\chi^2_{(1)}$=2.57	.11	n.s.	$\chi^2_{(1)}$=1.13	.29	n.s.
Anxiety Disorders	11	(61.1)	7	(38.9)	10	(58.8.)	5	(28.4)	$\chi^2_{(1)}$=0.02	.89	n.s.	$\chi^2_{(1)}$=0.35	.56	n.s.

Table 4.7 (continued)

	DBT-PTSD patients (n = 18)				CPT patients (n = 17)				Group differences T1			Test of treatment effects[b]		
	T1		T5		T1		T5							
Current Comorbidities	N	(%)	N	(%)	N	(%)	N	(%)	Test value (df)	p (two-tailed)		Test value (df)	p (two-tailed)	
Abuse Disorders	-		-		-		-		-			-		
Obsessive Compulsive Disorders	1	(5.6)	1	(5.6)	3	(17.6)	2	(11.8)	$\chi^2_{(1)}$=1.26	.26	n.s.	$\chi^2_{(1)}$=0.43	.51	n.s.
Somatization Disorders	1	(5.6)	1	(5.6)	1	(5.9)	1	(5.9)	$\chi^2_{(1)}$=0.00	1	n.s.	$\chi^2_{(1)}$=0.00	1	n.s.
Eating Disorders	4	(22.2)	2	(11.1)	1	(5.9)	0	0	$\chi^2_{(1)}$=1.91	.17	n.s.	$\chi^2_{(1)}$=2.00	.16	n.s.
Psychotropic Medication	N	(%)	N	(%)	N	(%)	N	(%)						
SSRI	4	(22.2.)	1	(5.6)	5	(29.4)	6	(35.3)	$\chi^2_{(1)}$=0.24	.63	n.s.	$\chi^2_{(1)}$=.4.83	.03	<.05
SNRI	5	(27.8)	5	(27.8)	3	(17.6)	2	(11.8)	$\chi^2_{(1)}$=0.51	.48	n.s.	$\chi^2_{(1)}$=1.40	.24	n.s.
Tricyclica	4	(22.2.)	4	(22.2.)	5	(29.4)	4	(23.5)	$\chi^2_{(1)}$=0.24	.63	n.s.	$\chi^2_{(1)}$=0.01	.98	n.s.
Neuroleptics	4	(22.2.)	1	(5.6)	4	(23.5)	4	(23.5)	$\chi^2_{(1)}$=0.01	.93	n.s.	$\chi^2_{(1)}$=0.03	.85	n.s.
Sedatives/Anxiolytics	-		-		-		-		-			-		
Mood Stabilizers	-		-		2	(11.8.)	2	(11.8.)	$\chi^2_{(1)}$=0.00	1	n.s.	$\chi^2_{(1)}$=0.00	1	n.s.

Note. CTQ = Childhood Trauma Questionnaire; DTS = Davidson Trauma Scale, BDI-II = Beck Depression Inventory II, CAPS-5 = Clinician Administered PTSD Scale for DSM-5, BSL-23 = Borderline Symptom List 23, ZAN = Zanarini Rating Scale for Borderline Personality Disorder, M = mean; SD = standard deviation; n.s.= not significant at a significance level of $p < .05$; [a]Participants age and education at pre-treatment;[b] Interaction effect between time (T1 vs. T5) and treatment group (DBT-PTSD vs. CPT).

Table 4.8 Behavioral and neural data of the Stroop interference scores in patients with complex posttraumatic stress disorder undergoing Dialectical Behavioral Therapy for PTSD and Cognitive Processing Therapy

	DBT-PTSD patients (n = 18)				CPT patients (n = 17)				Group differences T1			Test of treatment effects[b]		
	T1		T5		T1		T5		*Test value (df)*	*p (two-tailed)*		*Test value (df)*	*p (two-tailed)*	
Reaction Times in ms[a]	M	(SD)	M	(SD)	M	(SD)	M	(SD)						
Negative>neutral words	15.76	(38.51)	-0.72	(44.94)	22.67	(39.51)	19.74	(58.87)	$t_{(33)}$=0.24	0.81	n.s.			
Trauma>neutral words	77.10	(120.81)	24.93	(96.72)	96.63	(111.75)	29.60	(62.65)	$t_{(33)}$=0.41	0.69	n.s.	$F_{(2,66)}$ = 0.80	.45	n.s.
Color> neutral words	51.42	(96.17)	47.28	(98.48)	97.92	(104.64)	65.02	(91.08)	$t_{(33)}$=1.16	0.25	n.s.			
Accuracy (% correct)	M	(SD)	M	(SD)	M	(SD)	M	(SD)						
Negative>neutral words	-0.70	(2.07)	-0.79	(2.24)	-2.206	(8.76)	-3.49	(13.54)	$t_{(33)}$=0.71	0.48	n.s.			
Trauma>neutral words	2.22	(3.60)	1.67	(10.89)	-4.85	(11.01)	0.75	(5.02)	$t_{(33)}$=0.96	0.34	n.s.	$F_{(2,66)}$ = 0.27	.77	n.s.

Table 4.8 (continued)

	DBT-PTSD patients (n = 18)				CPT patients (n = 17)				Group differences T1			Test of treatment effects[b]		
	T1		T5		T1		T5		*Test value (df)*	*p (two-tailed)*		*Test value (df)*	*p (two-tailed)*	
Accuracy (% correct)	M	(SD)	M	(SD)	M	(SD)	M	(SD)						
Color> neutral words	-5.83	(11.68)	-4.83	(10.04)	-5.15	(9.32)	-4.44	(9.11)	$t_{(33)}$=0.19	0.85	n.s.			
Left Amygdala [MNI: -33, 2, -20]	M	(SD)	M	(SD)	M	(SD)	M	(SD)						
Negative>neutral words	0.14	(0.24)	0.07	(0.18)	0.08	(0.23)	0.01	(0.20)	$t_{(33)}$=0.77	.47	n.s.			
Trauma>neutral words	0.36	(0.43)	0.14	(0.20)	0.27	(0.35)	0.05	(0.22)	$t_{(33)}$=0.67	.51	n.s.	$F_{(2,66)}$ = 0.10	.99	n.s.
Color> neutral words	-0.05	(0.24)	0.05	(0.20)	-0.13	(0.32)	-0.01	(0.24)	$t_{(33)}$=0.79	.44	n.s.			
Right Insula [MNI: 30, 26, 13]	M	(SD)	M	(SD)	M	(SD)	M	(SD)						
Negative>neutral words	0.08	(0.19)	0.04	(0.14)	-0.02	(0.16)	0.08	(0.16)	$t_{(33)}$=1.67	.11	n.s.			
Trauma>neutral words	0.13	(0.16)	-0.04	(0.11)	0.07	(0.15)	-0.04	(0.19)	$t_{(33)}$=1.10	.28	n.s.	$F_{(2,66)}$ = 1.10	.34	n.s.
Color> neutral words	0.08	(0.12)	0.10	(0.10)	0.08	(0.16)	0.13	(0.13)	$t_{(33)}$=-0.09	.93	n.s.			
Right dlPFC [MNI: 45, 8, 37]	M	(SD)	M	(SD)	M	(SD)	M	(SD)						
Negative>neutral words	-0.02	(0.23)	0.06	(0.27)	0.02	(0.27)	-0.05	(0.27)	$t_{(33)}$=-0.47	.64	n.s.			
Trauma>neutral words	0.43	(0.36)	0.17	(0.31)	0.19	(0.47)	-0.05	(0.28)	$t_{(33)}$=1.74	.09	n.s.	$F_{(2,66)}$ = 1.17	.32	n.s.
Color> neutral words	0.31	(0.42)	0.53	(0.30)	0.40	(0.29)	0.38	(0.45)	$t_{(33)}$=-0.78	.44	n.s.			
Right dACC [MNI: 12, 44, 7]	M	(SD)	M	(SD)	M	(SD)	M	(SD)						
Negative>neutral words	-0.01	(0.21)	0.01	(0.20)	-0.06	(0.16)	0.05	(0.20)	$t_{(33)}$=0.90	.38	n.s.			
Trauma>neutral words	0.22	(0.36)	0.02	(0.18)	0.13	(0.34)	-0.05	(0.21)	$t_{(33)}$=0.70	.49	n.s.	$F_{(2,66)}$ = 0.57	.57	n.s.
Color> neutral words	0.04	(0.21)	0.11	(0.19)	0.02	(0.19)	0.07	(0.23)	$t_{(33)}$=0.27	.79	n.s.			

Note. cPTSD = Complex Posttraumatic Stress Disorder; M = mean; SD = standard deviation; n.s.= not significant at a significance level of $p < .05$; [a]Reaction times were log-transformed for analyses and refer to correct responses; [b]Interaction effect between time (T1 vs. T5), treatment group (DBT-PTSD vs. CPT) and condition (negative-neutral vs. trauma-neutral vs. color-neutral words); dlPFC=dorsolateral prefrontal cortex, dACC=dorsolateral prefrontal cortex.

Table 4.9 Correlations between changes on CAPS-5 symptom severity (Δ CAPS-5) with changes in Stroop performance (Δ reaction times, Δ correct Reactions) and brain activation (Δ brain activation in all of four clusters) from T1 to T5 in patients with Complex Posttraumatic Stress disorder undergoing Dialectical Behavioral Therapy for PTSD and Cognitive Processing Therapy

			Δ Reaction Times [a]			Δ Correct Reactions			Δ Amygdala activation			Δ Insula activation			Δ dlPFC activation			Δ dACC activation		
			neg> neu	tra> neu	col> neu	neg> neu	tra> neu	col> neu	neg> neu	tra> neu	col> neu	neg> neu	tra> neu	col> neu	neg> neu	tra> neu	col> neu	neg> neu	tra> neu	col> neu
DBT-PTSD (n=18)	Δ CAPS-5	Pearson Correlation	0.14	0.20	0.07	0.63	0.17	-0.01	0.12	0.05	0.04	0.43	0.12	0.11	0.25	0.30	0.10	0.12	0.33	-0.37
		Sig. (2-tailed)	0.60	0.42	0.78	0.01	0.48	0.96	0.67	0.83	0.87	0.07	0.63	0.66	0.30	0.21	0.68	0.65	0.18	0.12
CPT (n=17)	Δ CAPS-5	Pearson Correlation	0.15	-0.01	0.04	-0.19	-0.45	-0.10	0.01	0.58	0.15	-0.27	0.31	0.24	-0.26	0.06	0.03	0.01	0.13	-0.08
		Sig. (2-tailed)	0.58	0.96	0.89	0.48	0.06	0.69	0.97	0.01	0.54	0.28	0.21	0.35	0.30	0.81	0.91	0.98	0.62	0.76

Note. [a]Reaction times were log-transformed for analyses and refer to correct responses; neg=negative words, tra=trauma words, col=color words; dlPFC=dorsolateral prefrontal cortex, dACC=dorsolateral prefrontal cortex, DBT-PTSD= Dialectical Behavioral Therapy for PTSD; CPT=Cognitive Processing Therapy.

5 GENERAL DISCUSSION

Although approximately 70% of the general population experience a traumatic event during lifetime, only a small proportion develop PTSD (5.6%) (Benjet et al., 2016; Koenen et al., 2017). This fact motivated researcher to investigate individual differences as well as characteristics of the trauma itself that may both contribute to the development of PTSD. Epidemiological studies found evidence that the exposure to CM in contrast to adult-trauma is correlated to higher rates of PTSD than other types of trauma. Neurocognitive approaches have provided insight by identifying cognitive dysfunctions and associated functional and structural brain alterations that seem to differentiate PTSD samples from traumatized healthy individuals. This includes persistent enhancement of attention to (potential) threatening stimuli (hypervigilance) with impaired cognitive control mechanisms to inhibit emotional and cognitive responses (emotional interference). These alterations are discussed to be associated with heightened activity of limbic regions and altered activation in prefrontal regions leading to the typical symptom pattern of PTSD. Moreover, studies point to volumetric changes in PTSD patients as well as in healthy traumatized subjects in stress and emotion associated brain regions such as in the amygdala and in the hippocampus.

Although a cumulative (dose-dependent) effect can be assumed, the role of type and timing of CM has become of particular interest when investigating neurocognitive correlates contributing to psychopathology such as PTSD. Emerging evidence points to sensitive periods and specificity of CM-subtypes to differentially impact neurocognitive correlates in individuals with and without PTSD. However, research is still at a very early stage.

The development of PTSD in the aftermath of prolonged and severe CM is often associated with clinical features that extend beyond classic PTSD symptoms such as affective dysregulation, negative self-concept and disturbances in relationships. The diagnosis of cPTSD has therefore been included in the 11th revision of the ICD by the WHO. Numerous studies in adult-trauma PTSD patients have already provided evidence for neurocognitive alterations that may contribute to the development of psychopathology. However, the empirical database on neurocognitive correlates of cPTSD is quite limited at this time. Understanding alterations in cognitive and neural processes could optimize treatments in order to improve long-term outcomes of individuals with cPTSD. Several psychotherapeutic approaches have been developed for PTSD treatment and have been shown to be successful in treating PTSD symptoms as well as neurocognitive alterations. However, those treatments have mostly been

developed for survivors of adult-trauma PTSD. Meta-analyses demonstrated substantially lower effect sizes of psychotherapeutic treatments in CM-related cPTSD indicating poorer treatment response. Even though preliminary data point to the effectiveness of psychotherapy on normalizing neurocognitive correlates in cPTSD patients, these data are in clear need of replication.

To fill this gap, the aim of the doctoral thesis was to examine the long-term sequelea of CM with an emphasis on neurocognitive correlates of CM-related PTSD and cPTSD and the impact of psychotherapy on these measures. For this purpose, three experimental studies were conducted. Two studies investigated the role of CM and the influence of psychopathology (i.e., cPTSD) on functional and structural brain measures (study I and II). The third study aimed to examine whether 12 months of psychotherapy (DBT-PTSD or CPT) lead to improvement in neurocognitive alterations of cognitive control and emotional interference as investigated in study I.

In the following section, results of all three studies will be summarized and integrated into the context of previous research on neurocognitive correlates of cPTSD and the impact of psychotherapy. The following paragraph addresses methodological aspects and limitations of the studies and possible implications for future research are discussed.

5.1 Summary of Study Results and Integration into Previous Research

In **Study I**, we investigated the influence of CM and cPTSD on cognitive control and emotional interference during fMRI in 28 female patients with cPTSD, 28 TCs and 28 female HCs using a Stroop type paradigm. The inclusion of both control (TC and HC) groups provided us with the opportunity to explore whether neural alterations are associated with cPTSD symptoms or result from the experience of trauma alone.

As hypothesized, cPTSD patients exhibited increased Stroop interference, especially with trauma-related stimuli (reflected by slower reaction times and increased errors) compared to the other conditions and compared to both control groups (hypothesis a). In line with hypotheses b), patients with cPTSD showed increased dACC activation and a trend for increased insula activation during trauma-related stimuli compared to both control groups. Contrary to hypothesis b), we did not find higher amygdala activity in response to trauma-related words compared to neutral words in patients with cPTSD. Moreover, contrary to hypothesis c), our results further pointed in the opposite direction with greater dlPFC and vmPFC engagement in cPTSD patients during trauma-related words compared to both control groups.

Study II focused on the effects of CM on structural brain volume with an emphasis on the influence of type and timing of CM in a sample of 68 individuals exposed to prolonged CM with cPTSD (n = 42) and without cPTSD (TC; n = 26) symptomatology.

First, we found a negative correlation between global CM severity and bilateral amygdala volume. Interestingly, we could demonstrate that this effect was driven by the severity of neglect. Second, when contrasting cPTSD patients with TC subjects, the cPTSD group exhibited smaller bilateral amygdala volume, smaller right ACC volume and at trend smaller left ACC volume, while they did not differ regarding hippocampal volume. Third, we observed an effect of timing of CM exposure at 10-11 years of age and 13 years of age, for both bilateral amygdala and hippocampal volume. Fourth and regarding type x timing analyses, we observed sensitive periods during 10-12 years of age and 13-14 years of age for the severity of neglect, affecting right amygdala volume. Moreover, we found a sensitive period during 14 and 16 years of age for the severity of neglect affecting left amygdala volume. Likewise, we observed a sensitive time window for the severity of neglect during 9-13 years of age, affecting bilateral hippocampal volume.

Study III addressed the question whether neurocognitive alterations in cPTSD patients as measured in study I can be altered by 12 months of psychotherapy.

In line with our hypotheses, after 12 months of psychotherapy, cPTSD patients showed a), improved behavioral performance reflected in faster reaction times and less errors b), decreased activation in the amygdala and insula as well as c), decreased activation in the dACC and dlPFC during the processing of trauma-related words compared to neutral and negative words and compared to pretreatment. We did not find treatment-associated neural and behavioral differences between DBT-PTSD and CPT. For an overview of the study results, see Figure 5.1.

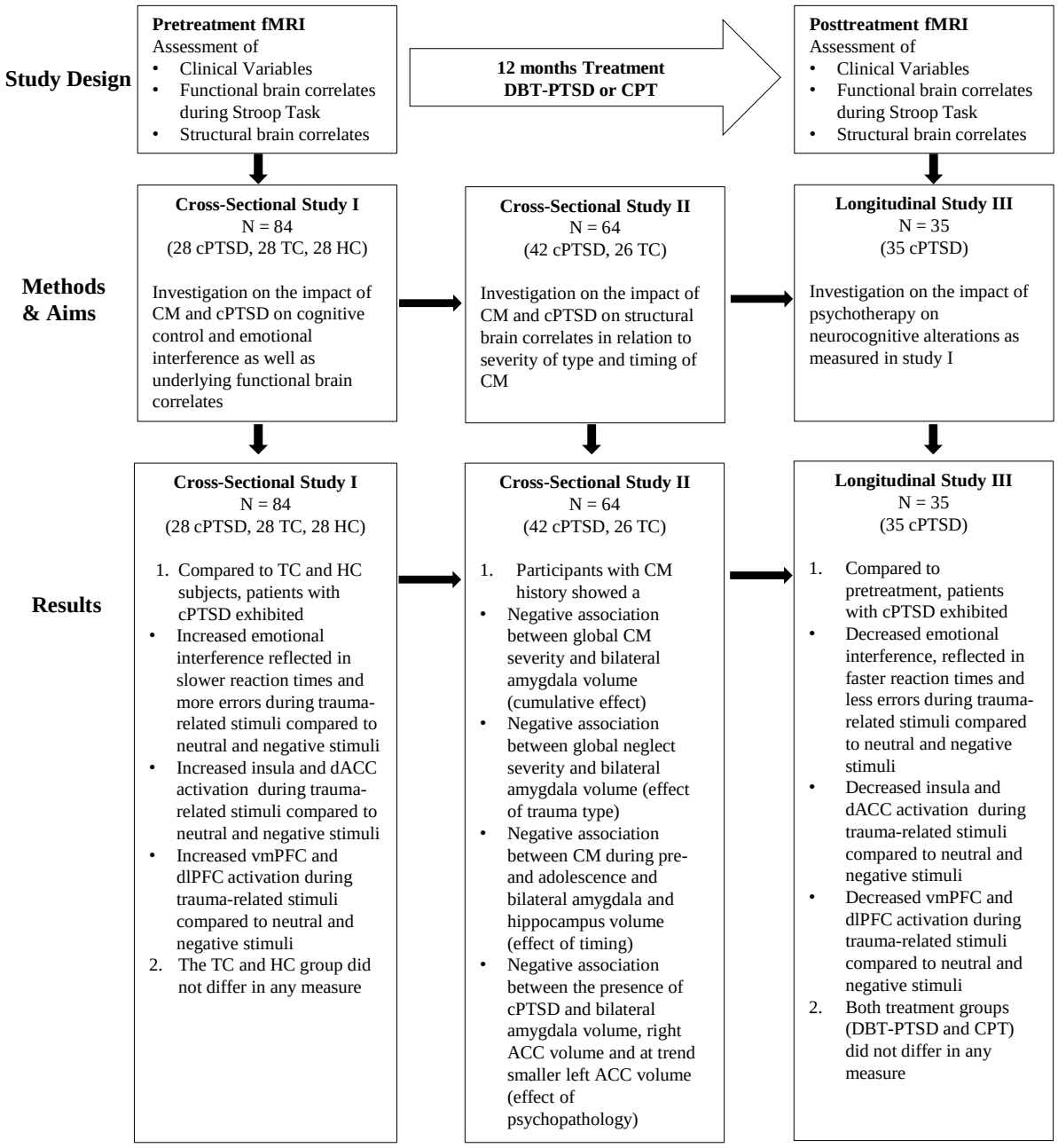


Figure 5.1 Results of the experimental studies

5.1.1 Neurocognitive Alterations are Differentially Affected by Trauma History –The Impact of Child Maltreatment as Compared to Adult-Trauma History

In Study I, we investigated the influence of CM and cPTSD on functional brain correlates of cognitive control. In line with our first hypothesis (hypothesis a), patients with cPTSD exhibited greater interference during the processing of trauma-related words as reflected in longer reaction times and increased errors as compared to neutral or negative words and as compared to both control groups. An amount of studies have found PTSD to be related to deficits across a variety of executive dysfunctions (Scott et al., 2015). However, dysfunctions in cognitive

control to inhibit automatic responses and gating distractions seem to be particularly relevant in PTSD (Vasterling & Hall, 2018). Although some studies have reported interference to other types of emotional stimuli (Hayes et al., 2012a), increased interference seems to be most evident when the distractor stimuli is of high valence (i.e., trauma-related) (Okon-Singer et al., 2015; Pessoa & Ungerleider, 2004; Song et al., 2017). From an evolutionary point of view, the fact that emotional stimuli capture one's attention is favorable: It enables the individual to react selectively and spontaneously to threatening environmental cues. However, this mechanism can become disadvantageous, when the processing of emotional but extraneous stimuli comes at the expense of goal-directed behavior (Iordan et al., 2013). In this regard, an amount of studies showed that threatening stimuli increase emotional interference in individuals with PTSD, such that they are slower in responding to target stimuli in the presence of trauma-relevant distractors (Zinchenko et al., 2017). It is not completely understood, if patients with PTSD show rather facilitated engagement towards threatening stimuli (Thomas et al., 2013; Wald et al., 2013) or impairments to disengage attention away from stimuli associated with threat (Aupperle et al., 2012; Gindt et al., 2017) or both (Vasterling & Hall, 2018). A recent review highlighted the role of the amygdala, dACC and insula cortex as important key nodes in the fear learning circuitry, suggesting that alterations within this system may contribute to enhanced salience and threat detection and contributing to PTSD psychopathology (Sheynin & Liberzon, 2017). As a consequence it has been suggested that this pattern may result in an interplay between enhanced emotional processing networks (SN; amygdala and insula) that serve to enhance attention towards emotional stimuli, and decreased inhibitory networks (CEN; dlPFC, vmPFC, mPFC) meant to disengage attention and redirect it to the task at hand (Henigsberg et al., 2019; Zinchenko et al., 2017). Contrary to this assumption and our second hypothesis (hypothesis b), we did not find higher amygdala activity in response to trauma-related words in patients with cPTSD. Moreover, contrary to the third hypothesis (hypothesis c), results further pointed in the opposite direction with greater dlPFC and vmPFC engagement in cPTSD patients during trauma-related words compared to both control groups. Since these results could have been explained by dissociative symptoms in patients (Nicholson et al., 2017), we correlated the observed results with dissociation scores, directly assessed before and after completing the Stroop task via the Dissociation Tension Scale (DSS-4; Stiglmayr et al., 2009). We did not find significant correlations between dissociation scores and any of our primary endpoints (behavioural and functional measures). These findings were initially surprising in light of previous studies pointing to impaired cognitive control reflected by increased activity within the amygdala and decreased activation in prefrontal brain networks (Dossi et al., 2020;

Henigsberg et al., 2019; Scott et al., 2015; Vasterling & Hall, 2018). On closer inspection, the contemporary neurobiological model of PTSD characterized by increased limbic and decreased prefrontal activation is mostly supported by results of studies that investigated PTSD patients with a trauma history during adulthood. Studies that have investigated neural correlates of cognitive control in individuals with PTSD related to CM and cPTSD, rather found increased dACC activation (Bremner et al., 2004; Thomaes et al., 2012) and dlPFC activation (Fonzo et al., 2016) in response to negative and trauma-related stimuli with no significant differences in amygdala activation (Bremner et al., 2004; Fonzo et al., 2016; Thomaes et al., 2012). Two studies in adolescents who had been exposed to early maltreatment used similar versions of a stop-signal paradigm and found increased activation in brain regions associated with cognitive control, including the dACC and lateral frontal regions during cognitive shifting and inhibitory responses (Carrion et al., 2008; Mueller et al., 2010). One might hypothesize that greater activation in these brain regions, which subserve cognitive control and emotional inhibition, reflect higher expenses of cognitive control resources in terms of a *compensatory mechanism* to correct for enhanced emotional interference towards trauma-related cues and a need to redirect attention to task-relevant demands (Comte et al., 2016). Nevertheless, patients showed poorer behavioral performance compared to TC and HC groups as measured in slower reaction times and more errors that could be interpreted as an inefficient compensatory effort to cope with trauma-related stimuli. On the other hand, one may argue that this compensatory effort enabled cPTSD patients to concentrate on task-relevant demands in order to complete the task, instead of being overwhelmed by trauma-related cues and panicked in the scanner. Against the background of the aforementioned studies in adult-trauma PTSD patients, showing an opposite pattern (Fani et al., 2019; Scott et al., 2015; Selemon et al., 2019), one may speculate that these discrepancies might be explained by the different trauma-samples that were investigated in those studies as compared to our studies.

Several studies point to a *qualitative difference* of PTSD/cPTSD related to CM compared to adult-trauma PTSD by the fact that CM is often accompanied by prolonged and repeated traumatization and raises the risk of further experiences of maltreatment (including physical, sexual and emotional abuse and/or physical and emotional neglect) (McCrory et al., 2017; McLaughlin et al., 2020). Because children are likely to spend a large majority of their time during the first years of life within the family or other caregivers, they are unable to escape ongoing traumatization. This may promote persistent fear and anticipation of recurrence, and thus requires an adaptation to a harmful environment (Cross et al., 2017; Teicher & Samson, 2016). In contrast to the deficient view of deleterious effects of stress on the brain, one may

interpret the findings of study I in a more evolutionary and developmentally informed view as an adaptation of neurobiological systems to an early hostile environment characterized by threat that may helped the child to react optimally and match the demands and challenges posed by the surroundings (Baldwin, 2013; Teicher et al., 2016). Albeit being adaptive in an unpredictable and hostile home environment, this early-established pattern of hypervigilance will likely become maladaptive in later life and other settings and might therefore increases the vulnerability for psychopathology (McCrory & Viding, 2015; Teicher & Samson, 2016). Since we did not compare patients with cPTSD related to CM and PTSD patients with a single traumatization during adulthood directly, the hypothesis of an adaptation process in patients with prolonged CM history needs further testing.

5.1.2 Neurocognitive Alterations are Differentially Affected by Child Maltreatment and Complex Posttraumatic Stress Disorder – the Impact of Cumulative Trauma Exposure

In study I, TC individuals did not show impaired performance towards trauma-related stimuli on both the behavioral and the neural level. We further did not find significant differences between the TC and HC group in any condition. Moreover, when contrasting cPTSD patients with TC subjects regarding structural brain correlates (study II), the cPTSD group exhibited smaller bilateral amygdala volume, smaller right ACC volume and at trend a smaller left ACC volume, while they did not differ regarding hippocampal volume. The current results suggest that these results are related to the presence of cPTSD and not to trauma exposure of CM itself. One could speculate that the TC group was not distracted by the trauma-related stimuli (study I), which in turn could be a crucial resilience factor that could prevent the development of cPTSD (Constans, 2005). These results are in line with studies pointing to an association between functional and structural brain alterations and the increased risk for developing psychopathology (for reviews see e.g.; Cross et al., 2017; McCrory et al., 2017; McLaughlin et al., 2020; Peverill et al., 2019; Sheridan et al., 2017; Teicher et al., 2016), albeit the temporal relationship is still not entirely clear. An alternative explanation might be the trauma history reported of the TC group as compared to cPTSD patients measured in study I and II. Contrasting both groups revealed that cPTSD participants reported more trauma types, a longer period of traumatization and greater severity of CM as compared to TCs (Table 3.5).

The latter explanation would be in line with a *cumulative (dose-dependent) model* of a progressive increase in risk for psychopathology, symptom severity and neurocognitive alterations associated with the number of trauma exposures (Evans et al., 2013; Felitti & Anda, 2010; Felitti et al., 1998). In this regard, one may hypothesize that an increased number and

severity of CM may lead to increased threat detection in the sense of an adaption for survival (Teicher et al., 2016) which is accompanied by functional and structural brain alterations (or vice versa) leading to maladaptive hypervigilance in the long run and contribute to the development of psychopathology. This interpretation is consistent with those studies suggesting that CM-related alterations in neurocognitive functions (DePrince et al., 2009; Gould et al., 2012; McLaughlin et al., 2019; Sheridan et al., 2017) appear to accumulate in a dose-dependent relationship during development, leading to an increased risk for the development of psychopathology (Cross et al., 2017; Dannlowski et al., 2012). As a response to a reviewer comment in study II, we examined structural brain alterations in two subsamples based on subjectively experienced resilience in a (preliminary) additional analysis. Subjects filled in the widely used resilience scale (Wagnild & Young, 1993). Based on the resilience score, we divided subjects into two groups (median split) and investigated the relationship between resilience and the severity of traumatization as well as brain volume. Experienced resilience was positively related to brain volume (no relationship for right hippocampal volume) whereby this relationship was observed exclusively within the more resilient group (all p's<.044). To further investigate the developmental trajectories, we visualized the severity of ACE overall, neglect and abuse for each participant, respectively and separately for subjects reporting more, or less resilience, pointing towards lower traumatization across the lifespan in those individuals reporting more resilience. Importantly, these findings mimic the aforementioned results of a cumulative relationship between trauma severity, functional and structural brain alterations and the development of psychopathology. Resilience and in line, protective factors are a highly important aspects and more thorough analyses in future studies are urgently needed. Moreover, due to the cross-sectional design of our study, our results are limited by an inability to disentangle the temporal and causal relationship of CM. Longitudinal studies are urgently needed to provide evidence for a potential neural pathway linking cumulative exposure to CM with neurocognitive alterations and the development of psychopathology such as PTSD.

5.1.3 Neurocognitive Alterations are Differentially Affected by Child Maltreatment and Complex Posttraumatic Stress Disorder – the Impact of Type and Timing of Trauma Exposure

In line with the assumption of a cumulative relationship of CM on neurocognitive correlates and psychopathology, we found a significant association between global CM severity and bilateral amygdala volume in study II. Importantly, this effect emerged by the severity of neglect. Moreover, when contrasting cPTSD patients with TC subjects, the cPTSD group

exhibited smaller bilateral amygdala volume, smaller right ACC volume and at trend a smaller left ACC volume, while they did not differ regarding hippocampal volume. We found no evidence for a significant association between global CM severity and hippocampal or ACC volume. These results are not in line with several studies, pointing to a negative relationship between global CM severity and hippocampal volume (Calem et al., 2017; Hanson et al., 2015; Saxbe et al., 2018; Teicher et al., 2012; Teicher & Samson, 2016) or ACC volume (Baker et al., 2013; Thomaes et al., 2010). However, several studies also failed to find reduced volume in the hippocampus or ACC when investigating the consequences of global CM severity (Landré et al., 2010; Lenze et al., 2008; Pederson et al., 2004; Veer et al., 2015). Importantly, several studies, however, found reduced hippocampal volume when investigating the differential impact of trauma type and timing of trauma exposure (Andersen et al., 2008; Teicher et al., 2018), supporting evidence for a *type and timing model* on neurocognitive correlates of CM (Dunn et al., 2018; Sheridan & McLaughlin, 2014). The type and timing model offers an alternative approach to the cumulative (dose-dependent) model suggesting a mainly linear function of cumulative CM exposure and neurocognitive alterations. Both models may not contradict each other but rather are complementary because alongside with the exposure to a variety of CM, the likelihood of exposure to a specific type of CM in a critical period increases as well (Schalinski & Teicher, 2015). For this purpose, Study II investigated the impact of CM on structural brain volume in relation to severity of type (i.e., severity of exposure to abuse and/or neglect) and timing of CM. We found that the negative association between global CM severity and bilateral amygdala volume emerged by the severity of neglect across traumatized individuals. In particular, greater exposure to neglect was associated with smaller bilateral amygdala volume and at trend with smaller bilateral hippocampal volume, while no associations were found for global abuse severity. These findings demonstrate the importance of considering the type of CM when investigating the relationship between CM and brain structures. Interestingly studies which found increased amygdala volume were mostly those that investigated brain volume in children or adolescence with chronically depressed mothers (Lupien et al., 2011), institutionally reared children (Mehta et al., 2009), or with a history of physical and/or sexual abuse (Morey et al., 2016). In contrast, smaller amygdala volumes were found among adults after severe forms of CM and diagnoses of BPD (Driessen et al., 2000; Schmahl et al., 2003; Schulze et al., 2016), Dissociative Identity Disorders (Vermetten et al., 2006) and PTSD (Ahmed-Leitao et al., 2016; Veer et al., 2015). These results may support the idea that severe CM may at first enhance amygdala sensitivity through dendritic growth and synaptic connectivity during childhood, as shown in rodents (Roozendaal

et al., 2009). Thereafter, repetitive activation may induce *wear and tear*, resulting in a smaller amygdala volume in adults with exposure to multiple and severe CM during life (Teicher & Samson, 2016; Veer et al., 2015; for meta-analyses see, Logue et al., 2018; Paquola et al., 2016). Additionally, we could replicate timing effects of CM on brain structure observed in previous studies (Andersen et al., 2008; Pechtel et al., 2014) in terms of sensitive periods, during which the exposure to CM has a maximally effect. In particular, we observed an effect of timing of CM exposure during preadolescence (10-11 years of age) and early adolescence (13 years of age) affecting both bilateral amygdala and hippocampal volume. Regarding type x timing analyses, we observed sensitive time periods during preadolescence (10 and 12 years of age) and adolescence (13 and 14 years of age) for the severity of neglect, affecting right amygdala volume. Moreover, we found a sensitive time period during later adolescence (age 14 and 16 years of age) for the severity of neglect affecting left amygdala volume. Likewise, we observed a sensitive time window for the severity of neglect during pre-and early adolescence (9-13 years of age) affecting bilateral hippocampal volume.

Importantly, the human brain shows neural plasticity throughout life (Hubener & Bonhoeffer, 2014; Lupien et al., 2009). However, neural plasticity has found to vary by the degree of maturation levels of brain regions (Brydges, 2016; Lupien et al., 2009). Heightened plasticity during different time windows is therefore not only accompanied by increased opportunities for development, but also accompanied by increased vulnerabilities. Neuronal plasticity occurs extensively, but not exclusively during the first years of life (Hubener & Bonhoeffer, 2014), as several studies found evidence for a sensitive period of heightened neuronal plasticity during (pre-) adolescence (Fuhrmann et al., 2015; Larsen & Luna, 2018).

More specifically, during (pre-) adolescence, white and grey matter undergo important maturation processes, particularly in frontal brain regions associated with higher-level cognitive processes (Fuhrmann et al., 2015) and in limbic regions such as in the hippocampus and in the amygdala (Semple et al., 2013; Toga et al., 2006). Furthermore, adolescence is characterized by marked endocrine changes such as increased hormonal stress reactivity within the HPA axis (Klein & Romeo, 2013). Against the background that limbic and several cortical brain regions play a key role in stress reactivity due to their high density of corticosteroid receptors, it seems reasonable to conclude that those brain structures are especially sensitive to stress during this time period (Brydges, 2016; Lupien et al., 2009). Importantly, and besides brain development, (pre-) adolescence as a sensitive period has also been observed for CM in fostering dissociative symptoms, PTSD symptoms (Schalinski & Teicher, 2015), depressive symptomatology (Khan et al., 2015), borderline symptomatology (Sharp & Wall, 2018), as well as susceptibility to

drugs (Kirsch et al., 2020), strengthening the idea that these time windows may be extremely vulnerable periods. The findings of sensitive and vulnerable time windows in (pre-) adolescence, however, are also likely windows of opportunity during which clinical interventions may provide maximal benefits to minimize or preempt long-term consequences of CM.

5.1.4 Targeting Neurocognitive Alterations of Complex Posttraumatic Stress Disorder Related to Child Maltreatment – The Impact of Psychotherapy

Based on the results of study I, study III addressed the question whether neurocognitive alterations of cognitive control and emotional interference in cPTSD patients can be altered by 12 months of psychotherapy with DBT-PTSD (Bohus et al., 2019) and CPT (Resick et al., 2016). In line with hypotheses a-c, cPTSD patients showed decreased emotional interference towards trauma-related stimuli together with decreased activation in the amygdala, insula, dACC and dlPFC during the processing of trauma-related words compared to neutral and negative words and compared to pretreatment. These results correspond with studies reporting decreased emotional interference on the behavioral level after treatment (El Khoury-Malhame et al., 2011; Joshi et al., 2020; Nijdam et al., 2018; Yang et al., 2019) and are in harmony with the notion that normalized fronto-limbic activation is a critical mechanism of symptom improvement in PTSD (Akiki et al., 2017; McTeague et al., 2017; Sheynin & Liberzon, 2017). The amygdala, insula and dACC, as core structures of the SN are involved in the intact as well as disordered detection of salient internal and external stimuli and emotional responding (Akiki et al., 2017; McTeague et al., 2017). The dlPFC as a center of the CEN is active during cognitively demanding tasks, goal directed behavior, and cognitive control of emotions in order to restructure cognitions or memories in reaction to perceived threat (Aupperle et al., 2013; Lindauer et al., 2008; Marwood et al., 2018; Thomaes et al., 2014) and has demonstrated greater activation in participants with PTSD undergoing emotion regulation tasks (Buhle et al., 2014; Joshi et al., 2020). Against this background, our findings of reduced emotional interference on the behavioral level, together with reduced amygdala, insula, dACC and dlPFC activation may point to lower fear processing within limbic regions and lower demands of prefrontal cognitive control networks to compensate for previously enhanced emotional interference. This may have resulted in decreased and *normalized* activation within those brain networks and regained mental capacity to respond appropriately when necessary (Joshi et al., 2020; Marwood et al., 2018). The results of study III provide support for the effectiveness of psychotherapy, in terms of regained capacity to differ between threat and safety, leading to a normalization of

maladaptive hypervigilance and a more composed dealing with trauma-related stimuli (Fonzo et al., 2017b; Fonzo et al., 2016). However, as we did not conduct a follow-up fMRI assessment, it remains to be shown if these neurocognitive changes last in the long-term.

Moreover, we observed changes in PTSD psychopathology, depression and BPD symptoms after treatment, suggesting that subjectively experienced symptoms improved over the course of treatment. However, symptom improvement did not correlate significantly with improvement in behavioral performance and changes in brain activation. Thus, evidence for a systematical relationship between symptom improvement following treatment and behavioral improvement as well as brain activation is still missing. Interestingly, we did not find significant differences on clinical and neurocognitive correlates between both treatment groups of DBT-PTSD and CPT, which is consistent with previous studies demonstrating the effectiveness of both treatments in cPTSD patients related to CM (Bohus et al., 2013; Granato et al., 2015; Resick et al., 2008). This might be interpreted in terms that both treatments, albeit using different techniques, may go hand in hand with specific improvements in emotional interference and cognitive control. For example, DBT-PTSD focuses on emotion regulation by *skills*. During intense conditions of stress and arousal, skills aim to interrupt automated dysfunctional emotional, cognitive and behavioral patterns (Bohus et al., 2019). Moreover, DBT-PTSD implemented trauma-specific cognitive and exposure-based techniques to alter dysfunctional trauma-related cognitions and emotions. CPT focuses on helping patients to change negative trauma-related beliefs by cognitive restructuring, especially with regard to guilt and denial (Bohus et al., 2019; Resick et al., 2016). Consequently, both types of intervention may have reduced trauma-associated fear responses by confronting patients with trauma-related details, memories, cognitions and beliefs leading. This habituation might be reflected in a more composed dealing with trauma-related stimuli reflected in decreased emotional interference and decreased fronto-limbic activation during the Stroop task. Further research is needed, which will be discussed in detail in section 5.2.2.

5.2 Important Limitations and Implications for Further Research

Several methodological aspects of the studies presented in this thesis have to be reviewed critically with regard to sample characteristics and the applied paradigms and designs.

5.2.1 Sample Characteristics

In all three studies, we only included female patients. Consequently, the results of our study are restricted to a female sample of cPTSD patients and cannot be generalized to male patients. We chose to focus on female participants, since several studies in PTSD in the general population have found higher rates of PTSD in women than in men (especially after CM) (Koenen et al., 2017). Moreover, studies have found gender-related differences in terms of brain activation in prefrontal and limbic regions during emotional and cognitive tasks (Lopez-Larson et al., 2011). Nevertheless, it will be important to replicate our findings in male patients. Moreover, we included medicated cPTSD patients in all studies. Several studies have investigated the effects of medication commonly used for depression and anxiety disorders (for example SSRIs) and have shown mixed results for the influence of medication on fMRI activation in the amygdala, insula and prefrontal brain regions (Delaveau et al., 2011; Fu et al., 2004; Harmer et al., 2006; Paulus et al., 2005; Rose et al., 2006; Schulze et al., 2016; van Tol et al., 2011), and behavioral patterns (Outhred et al., 2014; Paul et al., 2007; Schmitt et al., 2001). Therefore, we cannot completely rule out that medication effects might have confounded our results. To clarify the impact of medication on cognitive performance, emotion processing and corresponding fMRI activation in cPTSD, future studies would need to recruit drug-naive cPTSD patients.

Another limitation was the expected high rate of comorbid disorders, such as BPD, major depressive disorder and social anxiety in the cPTSD group. However, cPTSD after CM is associated with high comorbidity such as depression, interpersonal problems and anxiety as well as personality disorders (Cloitre et al., 2013; Green et al., 2010). Therefore, our sample is in this respect representative for this group of patients. Nevertheless, it could be argued that these comorbid disorders (especially BPD and major depression), rather than cPTSD accounted for the observed results in the current studies. To mitigate the potential influence of comorbid disorders, future research might study cPTSD patients, BPD, major depression and social anxiety disorders separately to strengthen the internal validity of findings regarding unique neurobiological pathways in the development of cPTSD. Finally, although cPTSD patients and TC individuals were matched for demographic parameters and age, patients with cPTSD reported more severe traumatic experiences compared to the TC group, as measured with the MACE and CTQ.

Even though, cPTSD has been included in the ICD-11 as a new diagnostic entity, a very topical debate focuses on the supposed construct validity of cPTSD (Achterhof et al., 2019; Cloitre et al., 2020; Ford, 2020). Two interesting studies by Achterhof et al. (2019) and Ford et al. (2020)

expressed concerns about methodological procedures in most of the studies on the construct validity of cPTSD (for studies on construct validity of cPTSD see, Cloitre et al., 2014; Elklit et al., 2014; Folke et al., 2019; Haselgruber et al., 2020; Karatzias et al., 2017; Kazlauskas et al., 2018; Kazlauskas et al., 2020; Knefel et al., 2015; Knefel et al., 2016; Liddell et al., 2019; Murphy et al., 2016; Palic et al., 2016; Perkonigg et al., 2016; Sachser et al., 2017; Zerach et al., 2019). Both mentioned studies did not find evidence for a clear distinction between a PTSD vs. cPTSD group (Achterhof et al., 2019; Ford, 2020). A major source of criticism of the diagnosis of cPTSD is the potential overlap between cPTSD and BPD for which prolonged or repeated trauma is also thought to be a risk factor. In fact, both cPTSD and BPD often share etiological risk factors such as CM as well as overlapping symptoms (e.g., problems in emotion regulation) (Resick et al., 2012) leading to high comorbidity rates of cPTSD and BPD (McLean & Gallop, 2003; Pagura et al., 2010). For further discussion, see Cloitre et al. (2020).
Moreover, a clear distinction should be made between CM-related PTSD and cPTSD, because CM survivors may also develop PTSD without cPTSD symptoms. In other words, cPTSD is not defined by type of trauma (i.e., CM) but rather by the symptom profile followed by trauma. Unfortunately, official diagnosis criteria of cPTSD were not available when our studies started. Therefore, inclusion criteria of the studies were defined such that they best reflect the clinical profile of cPTSD (Brewin et al., 2017; Cloitre et al., 2013) by including those with the diagnosis of PTSD (according to the DSM-5) following sexual or physical abuse before the age of 18 and meeting 3 or more criteria of BPD, including the criterion for affective instability. In a further study, it would be useful to validate the diagnosis of cPTSD in the current sample with the International Trauma Questionnaire (ITQ) and the semi-structured clinician-assessed International Trauma Interview (ITI) (Cloitre et al., 2018; Roberts et al., 2018). Moreover, further studies are needed to investigate specific neurobiological correlates with cPTSD by including different control groups (cPTSD patients vs. CM-related PTSD vs. adult-trauma PTSD patients) in order to identify brain circuits involved in the in the etiology associated with each disorder.

5.2.2 Study Design Characteristics

In all three studies, we investigated long-term neurobiological consequences of CM based on retrospective measures of CM. This investigation is challenged by several methodological factors. The distinct consequences of different types of CM (e.g., neglect and physical/sexual abuse) are difficult to distinguish from one another because they often co-occur (McLaughlin et al., 2020; McLaughlin et al., 2014). In addition, CM often occurs in a context of other

psychosocial stress factors, such as low socioeconomic status or parents with mental disorders and/or a history of CM in one´s own childhood, which themselves represent risk factors for the development of mental disorders and/or neurocognitive alterations in the growing-up individual (for meta-analyses see Assink et al., 2018; Assink et al., 2019; Mulder et al., 2018). Moreover, cross-sectional studies, in which patients are studied on different aspects (e.g., psychopathology, neurocognitive correlates) and retrospectively questioned about CM, are of limited significance with regard to the causal genesis. The validity of retrospective measures of CM has recently been discussed in a meta-analysis (Baldwin et al., 2019, for further discussion see, Widom, 2019), demonstrating poor agreement between prospective and retrospective measures of CM (Cohen $K_{\text{agreement-coefficient}} = 0.19$; 95% CI, 0.14-0.24; $p<.001$). In general, the authors recommended preferring prospective data in order to address causality. However, they also critically noted the lower sensitivity of prospective measures, as official records rather document severe cases of CM (Baldwin et al., 2019; Widom, 2019). Importantly, it was shown that agreement was higher when retrospective measures of CM were based on interviews rather than questionnaires and in studies with smaller samples sizes, which in turn applies to the studies in the present thesis.

One limitation of study I and III is the used paradigm of the cStroop and eStroop task. There has been a long debate if both tasks do measure exactly the same underlying processes: while the cStroop task measures inherent semantic or response conflict during incongruent trials, the eStroop effect has been discussed to reflect an attention bias towards emotionally charged words (Algom et al., 2004; Dalgleish, 2005; McKenna & Sharma, 2004; Phaf & Kan, 2007). However, more recent meta-analyses point to a shared neural network of both tasks, since both tasks involve the need to suppress responses to distracting word information and assess cognitive control during (emotional) interference (Cromheeke & Mueller, 2014; Song et al., 2017). Nevertheless, since both tasks strongly activate cognitive resources, they may not have been optimally suited to elicit treatment effects especially associated with emotion processing. Future studies could combine *symptom-provocation paradigms* (e.g., script-driven imagery; Negreira & Abdallah, 2019) with cognitive paradigms to assess treatment related emotional and cognitive improvements more differently.

Moreover, in study II we did not examine the relationship of observed structural brain alterations with other outcomes such as functional brain alterations or behavioral measures. Future studies are needed to investigate potential relationships between those measures.

An important limitation of study III is the lack of a significant relationship of symptom improvement following treatment with behavioral or neural changes. The lack of significance

may be a function of several causes, including lack of power and technical issues. For example, the Stroop task may not have been optimally suited as a measure of treatment outcome, as this task may not have enough sensitivity to elicit specific neural and behavioural correlates associated with symptom improvement. Moreover, the longitudinal sample was very selective (inclusion criteria: participation at fMRI at T1 and completion of 12 months of treatment) and characterized by a general improvement of symptoms. This may have led to too low variability in the sample to elicit significant correlations between symptom improvement, behavioural and neural measures. Additionally, changes in behavior, neural measures and cognition during an emotional response has been discussed to be loosely coupled (Bonanno & Keltner, 2004), and as such, a significant correlation is not necessarily observable, particularly in small sample sizes. With the given sample size of n=35, α=.05 and β=.05, a sensitivity power analysis conducted with G*Power (Faul et al., 2007) indicated that the smallest correlation that can be detected is a correlation ρ=0.52. This means that we cannot rule out correlations smaller than ρ=0.4 with sufficient certainty, given the sample size. Since small correlations are plausible yet, future studies with larger sample sizes are needed. Since we did not measure the TC group in a follow-up scanning session, we cannot rule out the possibility that behavioural and neural changes from pre- to posttreatment were due to habituation effects rather than treatment effects. Future studies including pre and follow up scans in both cPTSD and control groups are necessary to corroborate that treatment is indeed causal for improvement in behavioral measures and normalization in brain activation. We further could not show differences in neural or behavioral function between DBT-PTSD and CPT. Since DBT-PTSD has been found to be superior in the main RCT (Bohus et al., 2020), the lack of difference between treatment groups in our study may also have resulted from low statistical power due to participant dropout in the fMRI study. Consequently, future studies using randomized designs in conjunction with neuroimaging are needed to further delineate mechanisms of changes that are differentially attributable to both treatments.

5.3 Conclusion

The overall aim of this thesis was to identify the long-term sequelea of CM with an emphasis on neurocognitive correlates of CM-related PTSD and cPTSD and the impact of psychotherapy on these measures. The results of the present thesis provide further evidence that exposure to CM lead to long-term alterations in the neurobiological system of the individual. Especially severe and prolonged CM seem to be associated with a cumulative negative effect on neurocognitive correlates as reflected in increased emotional interference and altered brain

functions. While neurocognitive alterations (i.e., increased emotional interference towards trauma-related stimuli) were discussed to be adaptive in the short-term, they become maladaptive in the long run and may contribute to the development and maintenance of psychopathology. Moreover, we found evidence for a sensitive period during (pre-) and adolescence during which the exposure to CM and especially neglect significantly influence amygdala and hippocampus volume. These results strengthen the idea of a type and timing model of CM (as a complementary model to cumulative effects) in the understanding of neurocognitive alterations followed by CM and the development of psychopathology. After psychotherapy, increased emotional interference was found to be *normalized* in both neuronal and behavioral measures. It was concluded that psychotherapy helped patients by working with trauma-related memories, cognitions and emotions to integrate new adaptive information to distinguish between threat and leading to a normalization of maladaptive hypervigilance and a more composed dealing with trauma-related stimuli.

Due to our cross-sectional design, our results do not allow for insights into causal relationships. First, it remains an open question if functional brain changes in cPTSD patients underlie structural abnormalities or whether functional abnormalities induced long-term structural alterations. Second, it remains to be seen, whether neurocognitive alterations observed in cPTSD patients are a consequence of cPTSD, constitute a preexisting (genetic) vulnerability or reflect the interaction of both. Third, it is not fully understood to which degree observed structural brain alterations in both cPTSD and TC individuals may have led to the development of psychopathology or rather resilience. Forth, the impact of psychotherapy on neurocognitive measures requires further research. Going forward, the identification of factors related to psychopathology and resilience in the aftermath of CM is still a matter of central importance. Longitudinal studies are urgently needed to prospectively investigate pathophysiologic trajectories that link CM exposure during childhood and adolescence to adult psychopathology such as cPTSD. In this regard, it would be of high importance to prospectively investigate potential mediators of CM and their temporal or bidirectional effect at the neurobiological and epigenetic level (Agorastos et al., 2019). Understanding the pathways susceptible to disruption following CM and pathways leading to resilience following CM could help to better identify the individual risk for psychopathology, to individualize trauma treatments and could help to develop prevention strategies to reduce the deleterious long-term consequences of CM.

6 SUMMARY

Approximately 70% of the general population experience a traumatic event during lifetime. However, only a small proportion develop Posttraumatic Stress Disorder (PTSD) (5.6%). Considerable efforts have been made to investigate individual differences as well as characteristics of the trauma itself that both may contribute to the development of PTSD. The experience of child maltreatment (CM) in contrast to the experience of a traumatic event during adulthood has repeatedly found to be correlated to significant higher rates of PTSD. On a neurocognitive level, cognitive dysfunctions together with functional and structural brain alterations seem to characterize individuals with PTSD compared to traumatized healthy subjects. Although a cumulative effect of trauma can be assumed, the role of type and timing of CM has become of particular interest when investigating neurocognitive correlates contributing to the development of PTSD. Emerging evidence points to sensitive periods and specificity of CM-subtypes to differentially impact neurocognitive correlates in individuals with and without PTSD. However, research is still at a very early stage.

The development of PTSD in the aftermath of prolonged and severe CM is often associated with clinical features that extend beyond classic PTSD symptoms such as affective dysregulation, negative self-concept and disturbances in relationships. This complex form of PTSD (cPTSD) has therefore been included in the 11th revision of the World Health Organization's International Classification of Diseases (ICD-11). Numerous studies in PTSD patients related to various trauma types have already provided evidence for neurocognitive alterations. However, the empirical database on neurocognitive correlates of cPTSD is quite limited at this time. Understanding alterations in cognitive and neural processes could optimize treatments in order to improve long-term outcomes of individuals with cPTSD. Several psychotherapeutic approaches have been developed for PTSD treatment and have been shown to be successful in treating PTSD symptoms as well as neurocognitive alterations. However, those treatments have mostly been developed for survivors of adult-trauma PTSD. Meta-analyses demonstrated substantially lower effect sizes of psychotherapeutic treatments in CM-related cPTSD indicating poorer treatment response. Even though preliminary data point to the effectiveness of psychotherapy on normalizing neurocognitive correlates in cPTSD patients, these data are in clear need of replication.

To fill this gap, the aim of the doctoral thesis was to examine the long-term sequelea of CM with an emphasis on neurocognitive correlates of CM-related PTSD and cPTSD and the impact

of psychotherapy on these measures. For this purpose, three experimental studies were conducted. Two studies investigated the role of cPTSD and CM history on neurocognitive correlates. Study I investigated the role of psychopathology and CM history on functional correlates of cognitive control and emotional interference. Study II focused on the effects of CM on structural brain correlates with an emphasis on type and timing of traumatization. The third study aimed to examine whether 12 months of psychotherapy (DBT-PTSD or CPT) lead to an improvement of neurocognitive alterations in patients with cPTSD.

In study I, patients with cPTSD showed poorer behavioral outcome and an increased need for activation within prefrontal cognitive control networks, while confronted with trauma-related stimuli as compared to healthy controls with and without CM history. After 12 months of psychotherapy (study III), the pathologically increased emotional interference in cPTSD patients was found to be "normalized" on both neuronal and behavioral measures (reflected in faster reaction times, less errors and decreased activation within limbic and prefrontal brain regions). It can be concluded that psychotherapy helped patients by working with trauma-related memories, cognitions and emotions to integrate new adaptive information to distinguish between threat and safety to habituate towards trauma-related material.

Regarding structural brain correlates of CM, study II demonstrated a negative correlation between global CM severity and bilateral amygdala volume. Interestingly, this effect was driven by the severity of neglect. Moreover, results point to an effect of timing of CM exposure at 10-11 years of age and 13 years of age, for both bilateral amygdala and hippocampal volume. Regarding type x timing analyses, results revealed sensitive periods during 10-12 years of age and 13-14 years of age for the severity of neglect, affecting right amygdala volume. Moreover, results point to a sensitive period during 14 - 16 years of age for the severity of neglect affecting left amygdala volume. Likewise, a sensitive time window for the severity of neglect were identified during 9-13 years of age, affecting bilateral hippocampal volume.

The results of the present thesis provide further support that exposure to CM lead to long-term stress-induced cumulative changes in the neurobiological system. Moreover, the results provide further evidence for a type and timing model of CM, as a complementary approach in the understanding of the impact of CM across the entire lifespan on neurocognitive correlates. Longitudinal studies, however, are needed to get insight on causal relationships.

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