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Introduction and outline
INTRODUCTION

Working with people who experience severe psychological trauma leaves the therapist sometimes shocked about their horrifying, almost unbelievable histories and about the scars this may have caused, and at the same time intrigued by the way people were able to survive. In my daily practice, listening to details of a history of child abuse from a patient sometimes produces a film like image in my head for a while, which only represents a tiny proportion of the ongoing intrusions patients may suffer themselves. The way people cope with abuse histories is various, but most have missed a lot of opportunities in education, work experience and relationships in the past, because of the disturbed homes or environment they came from. For the therapist it is a challenge to support these people in their way to accept and take their past (“Vroeger”) seriously in the way it influenced their lives, emotions and bodies and at the same time go beyond (“Verder”) in order to optimally develop given the circumstances they came from.

A case history in short: In 2006 Nina came by the acute psychiatric services with panic attacks and depressive complaints after ending a long-lasting relationship. She visited a psychiatrist a couple of years who prescribed medication for a recurrent depressive disorder, but symptoms resisted. Three years later, when she was confronted with domestic violence at the neighbors and could not convince her psychiatrist from her distress, she deregulated in such a way that acute psychiatric service referred her to a part-time inpatient psychiatric ward where antidepressant medication has been prescribed again. She told that, years before she had discovered that she had repeatedly been sexually abused as a child by an employee of her father. Disclosing her history, she never received approval or support from her parents, who also demonstrated ambivalent behavior in her upbringing. Confronted with domestic violence in her neighborhood, she had been overwhelmed by emotions and intrusive memories of the sexual abuse. She was diagnosed next to the recurrent depressive disorder with a posttraumatic stress disorder and a vulnerable personality structure with fear for rejection and excessive need to control and esteem in DSM-IV terms, which refers to Complex PTSD. As background, she has a university degree and worked as office manager for years. However, she left different jobs and contracts were not prolonged, which she retrospectively associates with having problems with ambivalent employers and her high expectations for being valued in her work. Finally, she was not able to work anymore. Being very instable in affect regulation, she was not able to start directly with trauma exposure psychotherapy or EMDR. Therefore she started with a stabilizing group treatment based on psycho-education and cognitive behavioral therapy next to an individual treatment. She learned about survival strategies after chronic
repeated trauma. Analyzing cognitive patterns, knowing how to change these patterns and practical exercises to endure intense emotions, gave her tools to tolerate the sensations of these emotions. Complex PTSD complaints diminished and she felt more in control of her life. Then she started individual psychotherapy aimed at processing the details of the traumatic experiences. Six years after her first psychiatric contact, she receives monetary indemnity of a Criminal Injuries Compensation Fund because of her traumatic experiences. She starts volunteer work in a women organization, develops her creative talents and her self-esteem grows towards an independent woman.

For this thesis we investigated how people, who experienced chronic, repeated child sexual and/or physical abuse in intimate relationships and developed Complex posttraumatic stress disorder (Complex PTSD) up to adult life, can be scarred on the level of the brain. This study is a twin study with the study of Ethy Dorrepaal (VU, 2012) on the psychological effects of stabilizing treatment on Complex PTSD. We randomly assigned them to a treatment as usual or to - next to this treatment as usual - a treatment we named “Vroeger en verder” (“Before and beyond”), which is a stabilizing group treatment based on psycho-education and cognitive behavioral therapy, and investigated if psychological recovery was accompanied by normalization of structural or functional brain abnormalities in Complex PTSD.

1.1. PTSD and Complex PTSD

Sexual and physical child abuse appears to be a crucial etiological factor in the development of several psychiatric disorders such as posttraumatic stress disorder (PTSD). The risk of PTSD following exposure to any type of trauma is 10 to 20% with the highest risk associated with assaultive violence (Breslau et al., 1998). Sexual abuse affects 10% of Dutch women (Draijer, 1990). Child physical abuse and rape in women are far more likely to result in PTSD than other types of trauma (Kessler et al., 1995). Terr (Terr, 1991) divides trauma into two basic types: Type I psychotrauma refers to a single non-interpersonal traumatic event; type II psychotrauma refers to repeated and interpersonal traumatic events, such as child abuse.

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (APA, 2000), PTSD is characterized by a triad of symptom clusters: 1) intrusive symptoms, referring to the re-experiencing of traumatic events in thoughts, images or feelings as if the event occurs again, which can be accompanied by physical symptoms, such as trembling, transpiration, palpitations and shortage of breath, 2) avoiding of feelings and thoughts related to the trauma and numbing of feelings, and 3) hyperarousal, referring to an enduring alarm state,
leading to sleep and concentration problems, irritability with possible outbursts of anger, increased startle responses and over-alertness. Type II psychotrauma is associated with psychiatric symptoms that extend beyond the DSM-IV-TR 'simple' PTSD (Green et al., 2000). These more complex symptoms are described in following domains: I) problems in affect regulation (e.g. alteration between rage and affective emptiness, and impulsivity), II) dissociative symptoms (inability to remember certain periods of life, losing track of time, 'spacing out', feeling unreal), III) problems in self-perception (feelings of guilt and shame), IV) cognitions of the perpetrator (idealizing, revenge), V) relationships (inability to trust), VI) somatization and VII) loss of future perspectives. This syndrome has been brought under the heading of 'PTSD with associated features' in the DSM-IV-TR and is also known by clinicians as 'Complex PTSD' or 'Disorders of Extreme Stress Not Otherwise Specified' (DESNOS) (Ford, 1999; Herman, 1992; Pelcovitz et al., 1997; Zlotnick et al., 1996). Complex PTSD is associated with high co-morbidity on DSM-IV-TR Axes I and II, especially depressive and dissociative disorders on Axis I and borderline personality disorder (BPD) on Axis II (Ford & Kidd, 1998). In a student population prevalence of Complex PTSD was found to be 1% (Ford et al., 2006). It tends to run a chronic course in spite of considerable use of medical and psychiatric services (Höing, 2003).

Regrettably, there are far less imaging studies on child abuse than on adult abuse patients. Moreover, in the few imaging studies on child abuse related PTSD it is not reported if patients fulfill criteria for Complex PTSD or for criteria for common comorbid disorders in child abuse related PTSD such as depressive disorder, dissociative disorder or personality disorders. This thesis investigates for the first time brain structure and neurobiological correlates of declarative memory and attention in a well diagnosed child abuse related Complex PTSD population.

1.2. Structural brain abnormalities in PTSD

From a neurobiological perspective, PTSD is associated with structural and functional changes in limbic structures, in particular the medial temporal lobe (MTL) including the limbic system (Elzinga & Bremner, 2002; Sapolsky, 2000). Important limbic structures are the amygdala, a region associated with appraisal of danger and (conditioning of) fear responses, and the hippocampus, a key structure associated with declarative memory and contextualization of fear responses (Elzinga & Bremner, 2002; Sapolsky, 2000). A meta-analysis of 21 structural imaging studies on adults with chronic PTSD (Karl et al., 2006) revealed a significantly smaller left amygdala volume and significantly bilateral smaller hippocampus volumes, that decreased with PTSD severity. However, a number of magnetic resonance imaging (MRI) studies on PTSD have failed to
reveal hippocampal atrophy in specific groups, especially in children (De Bellis et al., 2002), recently traumatized people (Bonne et al., 2001), and elderly patients (Freeman et al., 2006; Golier et al., 2005; Yehuda et al., 2007), but also in early and lately traumatized patients (Fennema-Notestine et al., 2002; Jatzko et al., 2006; Pederson et al., 2004; Winter & Irle, 2004). Whether these negative findings are related to methodological issues or reflect pathogenetic differences is as yet unknown.

Whereas most structural MRI studies on PTSD have focused on MTL structures, it should be noted that these regions receive extensive inputs from other cortical areas involved in emotion processing or affect regulation (Rolls & Kesner, 2006), in particular the prefrontal cortex (PFC), orbitofrontal cortex (OFC), and the anterior cingulate cortex (ACC), and are thought to be critically involved in the pathophysiology of PTSD (Rauch et al., 2006). Affect regulation is usually be defined "as the set of control processes by which we influence, consciously and voluntarily, our emotions and how we experience and behaviorally express them" (…) "although a large body of data suggests that unconsciousness affect regulation is more essential than conscious emotion regulation in human survival functions" (Schore, 2009). In PTSD, ACC volumes were found to be reduced, both with voxel based morphometry (VBM) (Chen et al., 2006; Corbo et al., 2005; Kasai et al., 2008; Kitayama et al., 2006; Yamasue et al., 2003) and region of interest (ROI) based manual segmentation techniques (Kitayama et al., 2006; Rauch et al., 2003; Woodward et al., 2006). The ACC volume appeared to be inversely related to PTSD symptom severity (Yamasue et al., 2003).

The above-reviewed volumetric reductions in PTSD have been attributed to both environmental (i.e., stress) and genetic factors. Evidence from a human twin study (Kasai et al., 2008) suggests that ventral ACC losses would be stress induced or acquired via binding of the stress hormone cortisol to densely present glucocorticoid receptors in this structure (Conrad, 2008). With regard to hippocampal atrophy in PTSD the evidence is mixed. On the one hand, a twin study points at hippocampal atrophy as a genetically determined risk factor to develop PTSD rather than as a result of stress (Gilbertson et al., 2002). On the other hand, exposure to chronic stress and high cortisol levels have been shown to damage the hippocampus in prospectively designed animal studies (Sapolsky, 1996). Compatible with emerging evidence for neural plasticity (Sapolsky, 2003), successful pharmacotherapy for PTSD was associated with enlargement of the hippocampus (Vermetten et al., 2003).
Particularly early life stress, during a ‘window of susceptibility’, may have profound and enduring effects on the regulation of stress in later life. There is also evidence that different brain regions have unique periods of heightened sensitivity to the effects of early stress (Teicher et al., 2006). It has been shown that the risk for adult PTSD is higher after adult trauma (e.g. in veterans or abused women) if there has been child abuse as well (Clancy et al., 2006; Weisbart et al., 2008). A history of child abuse is related to increased neuro-endocrine stress reactivity, which is further enhanced when additional adult trauma is experienced (Heim et al., 2002). Although hippocampal volume was not different in a direct comparison of a small sample of child abuse related PTSD patients with patients after a single adult trauma (Bonne et al., 2008), the above-mentioned meta-analysis (Karl et al., 2006) revealed that child abuse had a greater impact on hippocampus volume than adult trauma and that motivated us to investigate specifically the way how child abuse morphologically effects the brain (Chapter 4).

1.3. Functional brain abnormalities in PTSD

1.3.1. Memory and emotion regulation

Intrusive memories (flashbacks, nightmares) and inability to recall aspects of the traumatic events (psychogenic amnesia) are among the key features of posttraumatic stress disorder (PTSD), impairing personal and social functioning (APA, 2000). There is evidence for an attention bias towards trauma relevant information in PTSD (McNally, 2006; Moore, 2009; Moradi et al., 2000), which may be related to intrusions interfering with attention for neutral information. In neuropsychological studies, performance on declarative memory tests with neutral stimuli has been found to be consistently impaired in PTSD (Brewin et al., 2007; Johnsen & Asbjornsen, 2008). Declarative memory (or explicit memory) refers to memories which can be consciously recalled such as facts (episodic memory) and to meaning or concept-based knowledge (semantic memory). In declarative memory tasks, generally patients are firstly exposed to words with a neutral, negative and/or a positive meaning and secondly tested to what extent they encoded and correctly recalled these words. In PTSD, declarative memory performance while processing emotional or trauma related material, is associated with functional changes in limbic and prefrontal brain areas (Elzinga & Bremner, 2002), that are all part of a network with extensive reciprocal connections (Liberzon & Sripada, 2008). According to fear conditioning models, PTSD is characterized by an exaggerated response of the amygdala to threat related stimuli, whereas activation is decreased in the medial prefrontal (PFC), orbitofrontal (OFC), and anterior cingulate cortex (ACC) as well as decreased activation in the hippocampus (Rauch et al., 2006). This model has been confirmed by neuroimaging studies with symptom provocation as well as with
cognitive activation paradigms (Bremner et al., 1999a; Bremner et al., 1999b; Bremner et al., 2003b; Bremner et al., 2003a; Bremner et al., 2004a; Driessen et al., 2004; Hendler et al., 2003; Protopopescu et al., 2005; Rauch et al., 2000; Semple et al., 2000; Shin et al., 1997; Shin et al., 1999; Shin et al., 2005). However, empirical data have been sparse and contradictory: functional imaging studies in PTSD have shown decreased as well as increased activation in the hippocampus and PFC, ACC and OFC (for review, see (Francati et al., 2007)). It is not clear to which extent trauma type and comorbidity, may affect these results. Neural correlates of declarative memory have been hardly studied in child abuse related PTSD and it is unclear whether the investigated samples included patients that met criteria for Complex PTSD. That is the reason for us to study emotional memory and its neurophysiologic correlates in child abuse related Complex PTSD (Chapter 2 and 3).

1.3.2. Selective attention and emotion regulation

Apart from declarative memory function, attention can also be negatively influenced by intrusive thoughts and feelings and this is likely to interfere with focusing attention to one's daily activities. Selective attention can be assessed with a well experienced test named the Stroop task. The classic version of this task involves naming the color of words printed in incongruent colors (e.g. the word “blue” printed in red) compared to prints in congruent colors (“red” printed in red). Increased classic Stroop “interference” refers to longer reaction times to incongruent stimuli and has repeatedly been found in PTSD (Kanagaratnam & Asbjornsen, 2007; Litz et al., 1996). Furthermore, in an emotional variant of the Stroop increased interference to trauma relevant material (e.g. “rape” printed in red) has been found in PTSD patients with various types of trauma compared to non-PTSD and non-trauma- exposed healthy controls (Bryant & Harvey, 1995; Field et al., 2001; Foa et al., 1991; Litz et al., 1996; McNally et al., 1990), although not in all studies (Kimble et al., 2009). Interference by trauma related material is supposed to be caused by triggering personal traumatic memories.

Imaging studies in healthy individuals have demonstrated activation in the anterior cingulate cortex (ACC) next to activation in the insula, left inferior frontal cortex, supplementary motor area (SMA), temporal cortex and striatum while performing the classic Stroop task (Pardo et al., 1990; Leung et al., 2000). The dorsal ACC is involved in emotion regulation and selective attention and has an important role in detection of response conflicts (Carter & van Veen, 2007). During the Stroop task, ACC activation serves as a warning signal for habitually reading the meaning of the words instead of naming the color of the words. PTSD veterans (Shin et al., 2001; Shin et al., 2007) and women with child abuse related PTSD (Bremner et al., 2004) showed increased dorsal ACC activation
compared to non-PTSD controls, in addition to decreased ventral ACC activation in an emotional Stroop task. A failure to activate the ventral ACC may reflect limited functional capacity relative to processing demands with compensatory dorsal ACC recruitment (Shin et al., 2001). With respect to the insula, conflicting findings have been reported: whereas PTSD veterans showed increased activation of the left anterior and bilateral insula during performance of the emotional Stroop task (Shin et al., 2001; Shin et al., 2007), women with child abuse related PTSD showed a relatively decreased insula activation compared to controls (Bremner et al., 2004a). The insula is involved in processing of intense emotions such as anger and disgust (Phan et al., 2002) and it could be argued that decreased insula activation in child abuse related PTSD indicates conscious avoidance or unconscious avoidance (dissociation) of affective states. Therefore, we studied selective attention and affect regulation in child abuse related Complex PTSD (Chapter 5).

1.4. Evidence based treatment for PTSD and Complex PTSD
While there is evidence of clinical improvement of anxiety disorders with pharmacotherapy and psychotherapy (Stein et al., 2006; Bisson & Andrew, 2007; Bradley et al., 2005), knowledge on neurophysiologic and anatomical underpinnings of these changes is still incomplete. Early neuroimaging studies demonstrated decreased glucose metabolism in the caudate nuclei (Baxter, Jr. et al., 1987) in obsessive-compulsive disorder (OCD) patients following successful pharmacotherapy, and similar changes were found after psychotherapy (Baxter, Jr. et al., 1992), suggesting greater plasticity of the brain than was formerly thought (Kandel, 1998). Since then imaging treatment outcome studies have been performed in various other anxiety and affective disorders (Etkin et al., 2005; Frewen et al., 2008; Linden, 2006; Quide et al., 2012; Roffman et al., 2005). Of these, posttraumatic stress disorder (PTSD) has received most attention from researchers, as it involves a clearly defined etiology and its pathogenesis can be elegantly explained from a glucocorticoid-stress model (Toffanin et al., 2011). According to this model, excessive and/or prolonged stress can result in dysregulation of the Hypothalamic-pituitary-adrenal (HPA) axis due to increased secretion of glucocorticoids. Increased binding to glucocorticoid receptors results eventually in damage of the hippocampus and prefrontal areas by impairing neurogenesis and leading to cell loss (Sapolsky, 2000) or reversible dendritic retraction (Conrad, 2008). In animal studies, evidence for neural plasticity (i.e. neural cell growth) in the hippocampus has been found (McEwen, 2001), and also in humans surgically treated for Cushing’s disease, a disorder involving pathologically increased cortisol secretion due to a pituitary adenoma (Toffanin et al., 2011). Therefore, the glucocorticoid-stress model may explain, at least in part, functional and morphological changes in stress related neuropsychiatric
disorders and their recovery. In healthy subjects, increased cortisol secretion stops after ending of the stressor, but hypercortisolemia tends to be prolonged in depressive disorders. Conversely, baseline cortisol is reported to be decreased in PTSD (Yehuda & Seckl, 2011), with emotional triggers giving rise to repetitive cortisol increases (Elzinga et al., 2003). However, decreased basal cortisol levels are specifically found in PTSD after child abuse (Yehuda & Seckl, 2011) and - according to a recent meta-analysis - only after physical or sexual abuse, and not after other trauma types (Meewisse et al., 2007). Time of trauma onset and the ongoing character of abuse might be more crucial in distinguishing abuse-related PTSD from other types of trauma. Therefore, in child abuse related Complex PTSD we would expect to find different abnormalities in brain morphology and/or function than in adult trauma related PTSD.

Clinical importance of the syndrome of Complex PTSD is its adverse effect on treatment outcome (Ford & Kidd, 1998): symptom severity of PTSD and presence of comorbid disorders is associated with high drop-out rates (McDonagh et al., 2005) and decreased efficacy of exposure (Foå et al., 2000) and Eye movement desensitization and reprocessing (EMDR) (Van Der Kolk et al., 2007). Comorbid axis II diagnoses call for more structured treatment (Cloitre et al., 2010; Lau & Kristensen, 2007) and predict worse outcome (Baars et al., 2011). Few studies investigate neural correlates of effective therapy and that is what we did in Chapter 5 and 6.

1.5. Outline of the thesis

The baseline part of this thesis (Chapter 2, 3, 4) attends to neurophysiologic changes after repeated child sexual and/or physical abuse in patients who are diagnosed with Complex PTSD with high rates of dissociative symptoms and comorbid depressive disorder and personality disorders, compared to non-trauma-exposed healthy controls. Chapter 2 describes a small sample of Complex PTSD patients and controls (9 vs. 9) of our pilot study; other chapters (3, 4 and also 5) refer to a larger patient sample (33 vs. 30) as part of our main (treatment) study.

In Chapter 2 we aimed to investigate declarative memory function and medial temporal lobe activation in 9 patients and 9 non-trauma-exposed healthy controls and to test organizational and methodological issues (pilot study). We focused specifically on the medial temporal lobe (MTL), including the hippocampus and amygdala, to increase power. We performed an event related functional magnetic resonance imaging (fMRI) during a verbal declarative memory task with neutral and negative words and compared performance (reaction times and error rates) and Blood Oxygenation Level Dependent (BOLD) signal...
changes between subjects with Complex PTSD and controls. Based on the fear conditioning model in ‘simple’ PTSD, we hypothesized that Complex PTSD patients would show worse declarative memory function with a preference for negative words relative to neutral words, and that this would be reflected by a decreased BOLD response in the MTL in patients compared to controls.

In Chapter 3 we aimed to investigate further declarative memory function in a new larger sample of 33 patients with child abuse related Complex PTSD and 30 non-trauma-exposed healthy controls, extending the previous pilot study. Specifically, we wanted to investigate how symptom severity and comorbidity affect neurocognitive functioning in PTSD. We simplified and adapted the emotional memory task to increase power and extended our regions of interest to the prefrontal cortex (PFC), considering its role in extinction and emotion regulation. Again we assessed performance and BOLD response (now whole-brain) differences. In addition, we explored whether any abnormalities were correlated with PTSD, trauma severity, and comorbid psychopathology, such as depressive, dissociative and borderline personality symptoms. We hypothesized that, as modeled in the fear conditioning model, Complex PTSD patients would perform worse than controls during a verbal declarative memory task, in particular for neutral words, and that this would be reflected by an increased BOLD response to negative words contrasted with baseline in the amygdala, and a decreased BOLD response in the medial PFC, OFC, and ACC, and in the hippocampus compared to controls.

In Chapter 4 we investigated if child abuse related Complex PTSD is associated with regional reduced brain volumes compared to healthy controls in the same sample (33 vs. 30) of Chapter 3, as was described in the PTSD literature. Again we explored whether any abnormalities were correlated with PTSD and/or trauma severity, or rather with comorbid dissociative, depressive and/or borderline personality symptoms. To this end, we compared regional gray matter (GM) density on a whole-brain voxel by voxel basis in patients with child abuse related Complex PTSD and matched non-trauma-exposed healthy controls and performed regression analyses using these clinical variables as covariates. We hypothesized that in child abuse related Complex PTSD volumes of MTL regions (hippocampus and amygdala) and ACC are reduced compared to healthy controls.

The second part of this thesis (Chapter 5, 6), investigates recovery of brain changes in (Complex) PTSD after treatment. Chapter 5 shows results of neurobiological treatment effects in a fMRI study (n = 16) using a classic and emotional Stroop task as part of the above mentioned treatment study, i.e. a randomized controlled trial (RCT). We aimed to investigate whether increased activation in
brain areas which are associated with error detection and emotional arousal, would normalize after effective treatment. We compared a stabilizing group treatment based on psycho-education and cognitive behavioral therapy (EXP) added to treatment as usual (TAU) with TAU only. Based on the literature, we hypothesized that at baseline, Complex PTSD patients would show increased interference during both classic and emotional Stroop tasks together with increased inferior frontal cortex, decreased ventral ACC, increased dorsal ACC and - because of high levels of dissociation (Bremner et al., 2004a) - decreased insula activation compared to controls. Furthermore, we expected Complex PTSD patients to show normalization of behavioral and neurophysiologic abnormalities following treatment, and to find correlations of change in PTSD severity with change in brain activation in the a priori regions of interest.

In chapter 6 we investigated in a systematic review whether neural correlates of PTSD normalized after successful treatment and if there are differences between adult trauma related PTSD and child abuse related Complex PTSD in this respect. We systematically reviewed imaging treatment outcome studies in adult patients with (partial) PTSD treated with pharmacotherapy, psychotherapy or other therapies in (Randomized) Controlled Trials or pre-post designs, excluding case studies form databases from PubMed, EMBASE, PsycINFO, PILOTS and Cochrane Library. I conclude with a general discussion in Chapter 7.