Memory traces of trauma: Neurocognitive aspects of and therapeutic approaches for posttraumatic stress disorder
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Chapter 1

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1.1 An introduction to trauma and memory

If the contents of this thesis were to be summarized in one sentence, I would say that it is about how traumatic events affect people and how they are remembered. In its most general definition, memory refers to our capacity for acquiring, retaining, and using information (McNally, 2003), and adequate memory functioning is therefore essential for human experiences. Dementia provides an illustration of the centrality of memory for the feeling of safety. An inability to remember or recognize can make people feel very unsafe and uncomfortable in familiar surroundings. In contrast to the remembering and recognition difficulties that characterize dementia, it is said that the core memory problem in trauma survivors with posttraumatic stress disorder (PTSD) is the inability to forget the danger of the situation they have experienced. They continue to feel unsafe, even though the danger is entirely in the past.

The minimalist approach to memory put forward by Eric Kandel (1976; 2009) has described different memory processes and their molecular basis in sea slugs (Aplysia). Simple memory processes in these animals such as sensitization and conditioning provided a meaningful illustration of how life threats lead to continuous stress responses and gave insight to the unconscious processes that play a role. It is adaptive that a sea slug shows a gill-withdrawal reflex in response to danger, but if this stress response continues for too long, the animal’s life is endangered. In an analogous way, trauma survivors with PTSD show a prolonged response to danger through ongoing hypervigilance and startle responses. This response is adaptive in a threatening situation, but is maladaptive in daily functioning, when the danger has passed. Several explanations have been offered for these processes in humans, such as dissociative reactions related to freezing in response to extreme stress (Nijenhuis, Vanderlinden, & Spinhoven, 1998), involvement of verbal and visual memory routes (Brewin, Dalgleish, & Joseph, 1996), as well as biological explanations with alterations in the stress response system and brain activation (LeDoux, 1996). In sum, the major disturbance in PTSD is that the memory of the trauma is coupled with psychological and physiological distress reminiscent of the response when the event occurred in real time (Yehuda, Joels, & Morris, 2010).

This thesis is about these “traces” engraved by a traumatic experience in memory. Certain details of the traumatic experience, such as the rifle of a gun, are remembered extensively and may continue to show up in the mind of the trauma survivor in forms of flashbacks and
nightmares, accompanied by intense emotions. Other details seem to have less priority in information processing and are easily forgotten, such as the order in which the events happened in a dangerous situation. Because of an extensive focus on danger, other daily memory tasks are constrained, resulting in a disrupted memory trace of trauma. The crucial question is: can these memory traces of trauma be resolved when the trauma survivor recovers? Can the feeling of safety originating from adequate memory functioning be restored by treatment? Can this be accomplished by a form of trauma-focused psychotherapy, and if so, which factors facilitate this process?

To investigate traumatic memory processes and how these were amenable to change, we studied a large sample of patients with PTSD and compared two treatments for PTSD with a different strategy to target the traumatic memory. One treatment has a traditional approach, in which the unresolved emotions evoked by the trauma are presumed to be active in memory and maintain the PTSD symptoms. By exposing the individual to the traumatic memories and learning from the trauma, the individual regains control and the anxiety response is normalized. The other method is based on a finding by chance, in which exposure to the traumatic memory alternated with distracting eye movements leads to desensitization. This procedure leads to a reduction in vividness and emotionality of the trauma memory (Gunter and Bodner, 2008; Engelhard, van Uijen, & van den Hout, 2010).

### 1.2 Epidemiology of posttraumatic psychopathology

Studies on consequences of traumatic events have a long history, but it was not until 1980 that PTSD was included as a diagnostic entity in the Diagnostic and Statistical Manual of Mental Disorders (DSM). The fourth edition of the DSM (DSM-IV-TR, APA, 2000) defines a trauma as an event, or events, in which the person has experienced, witnessed, or has been confronted with actual or threatened death or serious injury, or a threat to the physical integrity of oneself or others. Furthermore, the person’s response to that event involved intense fear, helplessness, or horror. From a survey conducted in the Netherlands, it became clear that 81% of civilians experience at least one potential traumatic event during their life (De Vries & Olff, 2009). Many acutely traumatized people have PTSD symptoms (such as nightmares, avoidance behaviour and startle reactions) in the weeks.
following the event, but most people will recover from these on their own within a few weeks post-trauma.

Contemporary cognitive models apply concepts of appraisal and coping to extreme stress to explain why some trauma survivors continue to endorse PTSD symptoms, whereas the majority of survivors do not. The appraisal of a potentially traumatic stressor as dangerous is essential in the occurrence of stress reactions and in whether they will subside or become chronic (Olff, Langeland, & Gersons, 2005). Also, the person’s coping with the initial stress reaction and the interpretation of later stress reactions determines whether or not they will continue to exist (Ehlers & Clark, 2000). In other words, the processes that lead to chronic PTSD can be characterized as very strong responses to a stressful event followed by inadequate mechanisms of recovery (Yehuda & LeDoux, 2007). Active coping and social support have proven to be important protective factors against PTSD symptoms, whereas negative coping is less helpful (Ozer, Best, Lipsey, & Weiss, 2003; Silver, Holman, McIntosh, Poulin, & Gil-Rivas, 2002; North et al., 1999). If the symptoms of reexperiencing, avoidance, and hyperarousal persist for one month or more, and if they impact the person’s work, education or social functioning, posttraumatic stress disorder is diagnosed (APA, 2000). The Dutch prevalence study showed that the lifetime prevalence of PTSD is 7.4% (De Vries & Olff, 2009). This prevalence rate of PTSD is comparable to those found in the US (Breslau et al., 1998; Kessler et al., 1995).

Specific PTSD symptoms overlap with symptoms of major depressive disorder (MDD). Sleep disturbances, diminished interest in activities and impaired concentration are present in the diagnostic criteria of both disorders. Depression and PTSD frequently co-occur; half of patients with PTSD also meet criteria for major depressive disorder (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; Shalev et al., 1998). Some PTSD experts therefore see MDD occurring in the context of PTSD as part of the same theoretical construct (O’Donnell, Creamer, & Pattison, 2004), but others argue that it has a separate underlying cause and pathophysiology (Yehuda, Vermetten, & McFarlane, 2012).

Definitions of trauma and PTSD are subject to change. The fifth edition of the DSM has just appeared in May 2013 (APA, 2013) and version 11 of the International Classification of Diseases is scheduled for approval in 2015. Criterion A2 (requiring intense fear, helplessness, or horror in response to the trauma) was removed from the definition of a traumatic event in DSM-5, because it has weak discrimination for who will or will not go on to developing PTSD after trauma (Friedman, Resick, Bryant, & Brewin,
Furthermore, the so-called ‘dysphoria’ symptoms, which show most overlap with MDD and often show up as a separate cluster in factor analyses (e.g., Olff, Sijbrandij, Opmeer, Carlier, & Gersons, 2009), were placed in a separate symptom category. The three clusters of symptoms were replaced by a four-factor model: intrusion symptoms, avoidance, alterations in cognitions and mood, and arousal symptoms. The 17 symptoms of DSM-IV were all included within the new categories, and three new symptoms were added: persistent and distorted blame of others, persistent negative emotional state, and reckless or destructive behavior. The ICD-11 proposal for PTSD is expected to simplify the diagnosis to make it easier for clinicians to use and more feasible in low-resource and humanitarian settings (Maercker et al., 2013). The ICD-11 criteria will probably only include the core symptoms of PTSD (reexperiencing, avoidance of reminders, and a perception of heightened threat), and remove the non-specific symptoms that are also part of other disorders.

1.3 The stress-response system

In understanding the impact of trauma and PTSD on survivors, it is helpful to take a more extended look at the stress response system. Fight-flight responses are automatically initiated by the brain when confronted with danger. According to LeDoux (1996), information about external stimuli such as sounds, images and smells are transferred to the amygdala in a fast, imprecise manner. Information is assessed as dangerous based on innate and previously learned experiences. Automatic responses, such as the startle response or fleeing from a dangerous situation, are generated. This pathway is called the subcortical route. During this process, the information about the external stimulus is also transferred to the cortex, which makes a more precise judgment whether the external stimulus is dangerous and how the person should respond to the stimulus. This cortical route takes more time.

Two hormonal systems, the sympathoandreno-medullar axis (SAM-axis) and the hypothalamic-pituitary-adrenal axis (HPA-axis) play an important role in regulating stress responses. These systems are responsible for the physiological symptoms when one is confronted with danger. Within the SAM-axis, the adrenal medulla is stimulated to release the hormones adrenaline and noradrenaline into the blood stream. They fasten heart rate, push up blood pressure and make glucose available in the blood stream. These hormones thus make the body ready for an optimal response to danger. After the fast activation of the central nervous system
by adrenaline and noradrenaline, the HPA-axis plays a role in regulating and maintaining the stress response over a longer period of time. Stimulated by the brain, the adrenal gland secretes the stress hormone cortisol. Cortisol functions to inhibit the stress response via a negative feedback loop to the hypothalamus and pituitary. It makes extra energy available for the stress reaction, stimulates the immune system, and inhibits the parasympathetic nervous system.

When experiencing a traumatic event, the amygdala and other paralimbic structures are thought to be excessively activated while the emotion regulating centers in the prefrontal cortex are insufficiently activated (Inslicht et al., 2011). These processes seem to be responsible for the peritraumatic stress reactions and for the prolonged perceived danger that many trauma survivors experience. If this system is not reset properly, PTSD symptoms may endure. Lindauer and colleagues (2004) have shown that medial prefrontal regions of the brain were indeed inhibited and parts of the limbic system were hyperactive in police officers with PTSD. In PTSD patients, the sensitivity of the noradrenergic system proved to be increased as well, expressed in heightened sympathetic nervous system activity (Elzinga, Vermetten, & Hovens, 2004). With regard to the HPA-axis, lower basal cortisol values were found to be associated with PTSD, as well as PTSD with comorbid depression, in a recent meta-analysis (Morris, Compas, & Garber, 2012). The type of trauma population and measuring circumstances influence HPA-axis results in PTSD patients (Meewisse, Reitsma, de Vries, Gersons, & Olff, 2007). Stronger feedback effects of cortisol, indicating enhanced sensitivity of the stress system, have been found quite consistently in PTSD populations (de Kloet et al., 2006), but also appear to be present in trauma-exposed control groups (Morris et al., 2012).

1.4 Information processing in PTSD: deficits in attention and memory

Information processing occurs partly consciously and partly subconsciously, and information is selected based on its importance for the person. Information about potential danger is very salient in this automated selection process, because it is linked to survival. Consequently, there is less capacity available for processing emotionally neutral material. The HPA-axis is also connected to the brain centers where information is processed and selected. Cortisol reaches the glucocorticoid receptors in the hippocampus, amygdala, and prefrontal cortex via the blood stream (Elzinga, Vermetten, & Hovens, 2004). Extreme or traumatic stress and reminders thereof may
therefore inhibit brain structures that support emotionally neutral information and autobiographical memory (e.g., the prefrontal cortex and hippocampus), while facilitating the operation of brain structures such as the amygdala that support emotional material and image-based memories (see for instance Bremner et al., 2003; Liberzon, Abelson, Flagel, Raz, & Young, 1999; Shin et al., 2004; Britton, Phan, Taylor, Fig & Liberzon, 2005; Simmons & Matthews, 2012).

Neuropsychological studies have examined trauma survivors with and without PTSD, and have compared them to control groups with people who have not experienced trauma. Several studies found attentional biases for trauma-related information, supporting the idea that information about perceived danger is preferentially processed in PTSD. Trauma words on a Stroop test resulted in slower color naming (e.g., McNally, Kaspi, Riemann, & Zeitlin, 1990; Thomaes et al., 2012) and trauma words in a dot-probe paradigm resulted in a faster reaction time (Bryant & Harvey, 1997). As for emotionally neutral information, the most prominent neuropsychological disturbances were found in the domains of sustained attention (Horner & Hamner, 2003), verbal memory (Brewin, Kleiner, Vasterling, & Field, 2007), and executive functioning (Polak, Witteveen, Reitsma, & Olff, 2012). The role of depressive symptoms was examined in some neuropsychological studies. Depressive symptom severity was found to be related to verbal memory performance (Sachinvala et al., 2000; Johnsen, Kanagaratnam, & Asbjørnsen, 2008), and to divided attention and working memory (Polak et al., 2012) in PTSD patients. However, the exact contribution of various psychiatric conditions that often co-occur with PTSD remains to be determined.

Dual representation theory of PTSD (Brewin, Dalgleish, & Joseph, 1996; Brewin, 2008) explains why especially verbal memory is impaired in PTSD. This theory presumes that there are two memory pathways that play a role in PTSD. In this model, the flashbacks experienced by PTSD patients are assumed to be the consequence of the enhanced encoding of certain aspects of the traumatic event, supported by a situationally accessible memory system (SAM) with a visual character. This explains why PTSD patients with flashbacks feel as if the trauma is occurring in the present, because the memory is primarily sensory and lacks a spatial and temporal context. Moreover, the model assumes that there is an impaired encoding of the material in the autobiographical, or verbally accessible memory system (VAM). According to Brewin (2008), this preferential encoding may be a product of peri-traumatic dissociation reactions and the prefrontal cortex temporarily going “off-line” in response to a level of stress that...
exceeds the person’s coping. Flashbacks would then provide an opportunity to encode the information that is lacking into verbally accessible memory, to create a new memory of the traumatic event with a spatial and temporal context. The awareness that the trauma has happened in the past would then also decrease the need for sensory memories in response to trauma cues. Dual representation theory suggests that the process of re-encoding from SAM to VAM does not take place in PTSD, leading to the persistent occurrence of flashbacks and nightmares and to a poorly functioning verbal memory system.

1.5 Information processing in PTSD: from trauma memories to clinical practice

Dual representation theory is one of the cognitive models that try to explain why certain trauma memories continue to be relived by PTSD patients, and other parts of the memories seem to go missing. Other theories have also studied these important ‘memory traces’ of trauma. A common feature in these theories is that certain aspects of the trauma are assumed to have a high priority in the automated selection process described above. According to some theories, these pieces of information give the trauma survivor clues what might be important situations to prevent repetition of the trauma in the future.

The theory of Horowitz (1976; 1983) already described how trauma survivors can experience the need to integrate new information accompanying the traumatic experience, but at the same time, the amount and nature of the information can be too much too comprehend. This would cause an alternating pattern between reliving (promoting the processing of the information) and avoiding (protecting the person by suppressing the threatening information). According to Horowitz, a stagnation of this process leads to persistent posttraumatic stress symptoms. Contemporary cognitive theories have pointed out that experiencing extreme stress, which depends on the person’s appraisal of the threat (Ehlers & Clark, 2000), is an essential factor in altering the memory processing of the event (Brewin, Dalgleish, & Joseph, 1996). Ehlers et al. (2002) found out that intrusive memories mainly represented stimuli that were present shortly before the moments of the trauma with the greatest emotional impact. Ehlers called these stimuli “warning signals”, because they alert the person to danger if encountered again. These stimuli are therefore logically connected with a sense of current threat.
Ehlers and colleagues (Ehlers, Hackmann, & Michael, 2004) also developed a therapeutic strategy in which the intrusions lead the therapist to the moments with the greatest emotional impact, also called “hotspots”. In trauma-focused cognitive behavioral therapy, they assume that it is essential to focus on hotspots and change their meaning in imaginal exposure sessions, in order to lead to a decrease in PTSD symptoms. Imaginal exposure techniques can also be combined with cognitive restructuring approaches for this purpose (Grey, Young, & Holmes, 2002). Addressing hotspots may be important in other trauma-focused psychotherapy methods as well, because in all these therapies emotional engagement with the trauma memories is assumed to be important for symptom reduction.

1.6 Therapeutic approaches for PTSD, predictors and outcomes

Several PTSD treatment guidelines recommend trauma-focused cognitive behavioural therapy (CBT) and eye movement desensitization and reprocessing therapy (EMDR; Shapiro, 1995) as first line treatments, because they have proven to be the most effective interventions to address traumatic memories and treat PTSD, and seem more effective than pharmacological treatments (NICE, 2005; Bisson et al., 2007; Foa, Keane, Friedman, & Cohen, 2008). Brief Eclectic Psychotherapy (BEP; Gersons, Carlier, & Olff, 2004) was included as a cognitive behavioural intervention in the NICE guidelines, because its treatment components overlap most with this approach. Multimodal, integrative treatments like BEP may be necessary to do justice to the various aspects of posttraumatic responses in realistic clinical settings (Schnyder, 2005). No well-powered studies have compared EMDR and BEP directly, nor has the response pattern been investigated to see whether one treatment is more efficient in targeting the traumatic memories than the other.

In trauma-focused psychotherapies, imaginal exposure to the traumatic event is applied to a greater or lesser extent, and this is probably an important mechanism of action (Bradley, Greene, Russ, Dutra, & Westen, 2005). It is, however, not quite clear which ingredients matter most in trauma-focused psychotherapy because all these therapies are built up of several potentially effective ingredients. Hotspots are an important concept in both BEP and EMDR. In EMDR therapy, imaginal exposure is focused on the hotspots of the traumatic event, followed by a distracting stimulus and free associations. In BEP therapy, the therapist focuses on a
detailed account of the hotspots of the traumatic event and usually one of these hotspots is addressed during an exposure session. It remains to be studied whether hotspots are related to treatment outcome.

In line with Grey & Holmes (2008), trauma-focused psychotherapies could also be called memory-focused psychotherapy for PTSD because therapists work with the memory of the traumatic event. To date, few studies have investigated the relationship between memory processes and successful trauma-focused treatment. This is remarkable, for it can be presumed that especially memory for verbal information is needed to benefit from trauma-focused psychotherapy. Wild and Gur (2008) measured verbal memory and other neuropsychological outcomes before a trauma-focused CBT, and found that lower verbal memory was related to poorer treatment outcome. Also, neuropsychological processes as outcome of trauma-focused psychotherapy have hardly been studied. Walter and colleagues (Walter, Palmieri, & Gunstad, 2010) showed that various trauma-focused interventions led to improvements in executive functioning. It is not clear whether these predictive effects and outcomes are restricted to specific trauma-focused psychotherapy methods, or for all methods in the same magnitude.

In addition, neuroendocrine parameters have hardly been studied in association with treatment outcome in trauma-focused psychotherapy. One study compared PTSD patients who did and did not respond to trauma-focused CBT and found the activity of a cortisol metabolite, 5α-reductase, to be lower in non-responders (Yehuda et al., 2009). Baseline cortisol levels did not appear to be related to treatment outcomes of trauma-focused CBT (Yehuda et al., 2009) or BEP (Olff, de Vries, Güzeltan, Assies, & Gersons, 2007).

1.7 Aim and questions of the study

With this study we were interested in whether PTSD and its clinical and neuropsychological correlates can be treated and reversed by means of BEP and EMDR. BEP and EMDR consist of a different set of therapeutic techniques, and we studied the effects of the treatments on various clinical and neuropsychological outcomes. We also wanted to investigate which groups of PTSD patients benefit most from trauma-focused psychotherapy, as it is not yet clear which treatment works best for whom. This may help to refine treatment planning and delivery, in order to meet the treatment needs of specific groups of patients (Karatzias et al., 2007). Figure 1 indicates the neuropsychological, neurobiological, and autobiographical
memory correlates of PTSD that will be examined for this aim. The shaded lines indicate the relationships studied in this thesis. Finally, we wanted to determine whether neuropsychological impairments are specifically attributable to PTSD, or to co-morbid symptoms and psychiatric conditions. PTSD is frequently accompanied by (symptoms of) major depressive disorder and other conditions. Therefore, it is important to disentangle the influence of these factors in neurocognitive functioning.

Figure 1. Neurocognitive and neuroendocrine processes in PTSD and possible relationships to treatment outcome
In sum, the studies in this thesis are designed to answer the following questions:

- Are neurocognitive deficits in trauma survivors and PTSD patients specifically related to PTSD, or also to its clinical correlates such as major depression and sleep disturbances?
- What are the effects of BEP and EMDR on PTSD and its clinical correlates, and is there a difference in response pattern?
- Do neurocognitive disturbances in PTSD change over the course of trauma-focused psychotherapy?
- Can predictors be identified for treatment success in trauma-focused psychotherapy? Do neurocognitive and neuroendocrine aspects of PTSD and hotspots in trauma memories contribute to treatment response?

1.8 Design of the study

With the exception of the study on sustained attention, all studies of this thesis are based on data from a randomized controlled trial that compared BEP with EMDR in 140 patients with PTSD. Data are reported from the pre-treatment assessment, two post-treatment assessments and session-by-session measurements. Structured clinical interviews and questionnaires were administered at all major assessment points. Self-reported PTSD symptoms were the primary outcome measure, and were assessed during all measurements and sessions within the first eighteen weeks of the trial. Neuropsychological assessments were performed at pre-treatment and at the second post-assessment. A subsample of the randomized participants of both treatment conditions (n=26) completed additional neuroendocrine measures at home after the pre-treatment assessment and the second post-assessment. Figure 2 shows the design of the randomized trial.

Data from the study on sustained attention stem from a subsample (n=135) of a large prospective health monitoring study after the fireworks disaster in Enschede, the Netherlands (Meewisse, Olff, Kleber, Kitchiner, & Gersons, 2011; Van Kamp & van der Velden, 2001). The disaster took place on May 13, 2000. Two years after the disaster, participants completed structured clinical interviews and questionnaires and sustained attention was measured by means of a neuropsychological measure.
1.9 General outline of this thesis

Neuropsychological impairments in PTSD can be a consequence of several mental health symptoms and disorders that are frequently present in trauma survivors and PTSD patients. Chapter 2 compared patients with PTSD and a comorbid major depressive disorder to PTSD patients without major depressive disorder to find out if they differ in terms of their performance on tasks of verbal memory and executive functioning. In chapter 3, a study is described on sustained attention in disaster survivors. Partial correlations were computed, investigating the extent to which sustained attention performance was related to PTSD symptoms, depressive symptoms and sleep disturbances.

Sufficiently large randomized controlled trials are recommended by PTSD treatment guidelines to provide evidence on the comparative effectiveness of the various therapies and to provide more information about the type and duration of the effective interventions (NICE, 2005). Chapter 4 describes the main outcomes of the randomized controlled trial.
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comparing BEP and EMDR treatment. Self-reported symptoms of PTSD, depression and general anxiety were assessed during this trial as well as clinician-rated PTSD and co-morbid psychiatric conditions. Response patterns were also compared for BEP and EMDR. Chapter 5 is a case report of one of the patients in the trial, who had a diagnosis of PTSD and obsessive-compulsive disorder (OCD). Zooming in on the trauma story and treatment of this patient, this report hopes to contribute to an understanding of the therapeutic mechanisms involved in treatment of these often co-occurring conditions. In chapter 6, verbal memory and executive functioning are examined over the course of trauma-focused psychotherapy. This part of the study investigates if changes in neuropsychological functioning are present in both treatment conditions and if changes in symptom severity correlate with changes in verbal memory and executive functioning.

With the aim of determining which treatment works best for whom, several potential predictors were investigated in relationship to treatment outcome for BEP, EMDR, or both. Chapter 7 investigates the association between baseline verbal memory performance and decrease in self-reported PTSD during trauma-focused psychotherapy. In this part of the study we also investigate if we can correctly classify patients as responder based on their pre-treatment memory performance. In chapter 8, audio recordings of successful and unsuccessful BEP therapies are coded for the presence of hotspots in imaginal exposure sessions. This pilot study discusses how therapists can address hotspots in several forms of trauma-focused psychotherapy. Chapter 9 investigates HPA-axis functioning in relationship to treatment outcome in a subsample of the participants of the randomized controlled trial.

In chapter 10, the results of all previous chapters will be summarized and discussed. This final chapter describes the limitations of the studies, as well as clinical implications, and suggestions for further research.

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National Institute for Health and Clinical Excellence.


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