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

Nijdam, M.J.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (http://dare.uva.nl)

Download date: 09 Sep 2019
In the Netherlands, 81% of the general population experiences at least one potentially traumatic event in their life, such as a traffic accident, assault, rape, or disaster. Around 7% of people fulfill the criteria for posttraumatic stress disorder at some point during their life. Certain details of the traumatic experience, such as the rifle of a gun, are remembered extensively by these survivors and may continue to show up in their mind 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. Because of the continued focus on danger, less capacity is available for daily memory functioning. The aim of this thesis is to investigate these "traces" engraved by a traumatic experience in memory and to examine how they are amenable to change by psychological therapy.

Mirjam Nijdam (1980) is a psychologist and researcher affiliated with the Department of Psychiatry at the Academic Medical Center at the University of Amsterdam since 2003. Currently she works as a postdoc researcher and healthcare psychologist in training.

ISBN: 9789088916687
MEMORY TRACES OF TRAUMA:
NEUROCOGNITIVE ASPECTS OF AND
THERAPEUTIC APPROACHES FOR
POSTTRAUMATIC STRESS DISORDER
A contribution to the printing costs of this dissertation was provided by the Graduate School of the Academic Medical Center at the University of Amsterdam, which is gratefully acknowledged.

© 2013 Mirjam Nijdam, Amsterdam, The Netherlands
ISBN: 9789088916687

Cover illustration: Avantia Damberg
Cover design: Proefschriftmaken.nl || Uitgeverij BOXPress
Printed by: Proefschriftmaken.nl || Uitgeverij BOXPress
Published by: Uitgeverij BOXPress, 's-Hertogenbosch
MEMORY TRACES OF TRAUMA: NEUROCOGNITIVE ASPECTS OF AND THERAPEUTIC APPROACHES FOR POSTTRAUMATIC STRESS DISORDER

ACADEMISCH PROEFSCHRIFT
ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. D.C. van den Boom
ten overstaan van een door het college voor promoties ingestelde commissie, in het openbaar te verdedigen in de Agnietenkapel
op dinsdag 17 september 2013, te 10.00 uur

door Mirjam Jemina Nijdam
geboren te Amsterdam
Promotiecommissie

Promotores: Prof. dr. M. Olff  
Prof. dr. B.P.R. Gersons

Overige leden: Prof. dr. W. van den Brink  
Prof. dr. M.A.G. Sprangers  
Prof. dr. M.A. van den Hout  
Prof. dr. B.A. Schmand  
Prof. dr. M.A. Grootenhuis  
Prof. dr. U. Schnyder

Faculteit der Geneeskunde
Nunca sei como é que se pode achar um poente triste.
Só se é por um poente não ser uma madrugada.
Mas se ele é um poente, como é que ele havia de ser uma madrugada?

Ik heb nooit begrepen hoe men een zonsondergang treurig kan vinden.
Hoogstens omdat een zonsondergang geen zonsopgang is.
Maar als het nu een zonsondergang is, hoe zou het dan een zonsopgang moeten zijn?

Fernando Pessoa (8.11.1915)
CONTENTS

Chapter 1. Introduction................................................................................................. 9

Chapter 2. The role of major depression in neurocognitive functioning in patients with posttraumatic stress disorder ......................................................... 29

Chapter 3. Disaster-related posttraumatic stress symptoms and sustained attention: Evaluation of depressive symptomatology and sleep disturbances as mediators ........................................................................................................... 43


Chapter 5. Treatment of sexual trauma dissolves contamination fear: case report ....................................................................................................................... 77

Chapter 6. Neurocognitive functioning over the course of trauma-focused psychotherapy: changes in verbal memory and executive functioning...... 85

Chapter 7. Pretreatment low verbal memory is related to worse response to trauma-focused psychotherapy for posttraumatic stress disorder....... 107

Chapter 8. Hotspots in trauma memories and their relationship to successful trauma-focused psychotherapy: a pilot study ......................... 125

Chapter 9. Dexamethasone-suppressed cortisol awakening response predicts treatment outcome in posttraumatic stress disorder............. 141

Chapter 10. Discussion.............................................................................................. 153

Summary .................................................................................................................. 175
Samenvatting......................................................................................................... 182
Dankwoord ......................................................................................................... 190
Curriculum Vitae ................................................................................................. 195
List of publications.............................................................................................. 197
Portfolio ............................................................................................................... 200
Chapter 1

Introduction

Memory traces of trauma
9
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, 2000).
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; Johnson, 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
Memory traces of trauma
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, Güzelcan, 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.
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.

References
Bisson, J.I., Ehlers, A., Matthews, R., Pilling, S., Richards, D., & Turner, S.


Chapter 1

Introduction


Inslicht, S.S., Otte, C., McCaslin, S.E., Apfel, B.A., Henn-Haase, C., Metzler,
Chapter 1

Introduction


Meewisse, M.L., Reitsma, J.B., De Vries, G.J., Gersons, B.P.R, & Olff, M.
Chapter 1

Introduction

Memory traces of trauma


Sachinvala, N., Von Scotti, H., McGuire, M., Fairbanks, L., Bakst, K., McGuire,


Yehuda, R., Bierer, L.M., Sarapas, C., Makotkine, I., Andrew, R., & Seckl, J.R.


The role of major depression in neurocognitive functioning in patients with posttraumatic stress disorder

Abstract

**Background:** Posttraumatic stress disorder (PTSD) and major depressive disorder (MDD) frequently co-occur after traumatic experiences and share neurocognitive disturbances in verbal memory and executive functioning. However, few attempts have been made to systematically assess the role of a comorbid MDD diagnosis in neuropsychological studies in PTSD.

**Objective:** The purpose of the current study is to investigate neurocognitive deficits in PTSD patients with and without MDD. We hypothesized that PTSD patients with comorbid MDD (PTSD+MDD) would have significantly lower performance on measures of verbal memory and executive functioning than PTSD patients without MDD (PTSD–MDD).

**Method:** Participants included in this study were 140 treatment-seeking outpatients who had a diagnosis of PTSD after various single traumatic events and participated in a randomized controlled trial comparing different treatment types. Baseline neuropsychological data were compared between patients with PTSD+MDD (n=84) and patients with PTSD–MDD (n=56).

**Results:** The PTSD+MDD patients had more severe verbal memory deficits in learning and retrieving words than patients with PTSD alone. There were no differences between the groups in recall of a coherent paragraph, recognition, shifting of attention, and cognitive interference.

**Conclusions:** The results of this study suggest that a more impaired neurocognitive profile may be associated with the presence of comorbid MDD, with medium-sized group differences for verbal memory but not for executive functioning. From a clinical standpoint, being aware that certain verbal memory functions are more restricted in patients with comorbid PTSD and MDD may be relevant for treatment outcome of trauma-focused psychotherapy.
Chapter 2
The role of major depression in neurocognitive functioning in patients with posttraumatic stress disorder

Introduction

Posttraumatic stress disorder (PTSD) and major depressive disorder (MDD) are common outcomes after experiencing a traumatic event (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995), with considerable overlap in their symptomatology. Sleep disturbances, diminished interest in activities, and impaired concentration are shared diagnostic criteria of these disorders in DSM-IV. Therefore, it is not surprising that the comorbidity of these disorders is high; approximately 50% of PTSD patients also meet criteria for MDD (Kessler et al., 1995; Shalev et al., 1998). Some investigators see symptoms diagnosed as comorbid depression as reflecting the construct of PTSD (O’Donnell, Creamer, & Pattison, 2004), whereas others have found support for separating core PTSD symptoms from dysphoria symptoms (Rademaker et al., 2012).

Neuropsychological studies have consistently confirmed disturbances in concentration or sustained attention in different trauma populations with PTSD (Horner and Hamner, 2003), as well as consistent deficits in verbal memory (Brewin, Kleiner, Vasterling, & Field, 2007) and executive functioning (Polak, Witteveen, Reitsma, & Olff, 2012). Major depression in itself is also associated with several neurocognitive deficits, which are most pronounced in mental flexibility, control, and effortful processing (Veiel, 1997). These neuropsychological disturbances can be measured in a way that closely approximates the difficulties that patients face in their daily lives, such as remembering a grocery list, summarizing a newsflash they just heard on the radio, inhibiting irrelevant information while performing a certain task, and performing multiple tasks at a time.

In PTSD populations, few attempts have been made to systematically assess the role of a comorbid MDD diagnosis in neuropsychological studies. So far, in most studies the severity of depressive symptoms has been examined instead of the diagnosis. Sample sizes in these studies were mostly small and therefore have an increased risk of false-negative findings. Sachinvala et al. (2000) investigated the role of depressive symptoms in neuropsychological performance of Vietnam veterans with chronic PTSD and found that depressive symptoms negatively correlated with memory performance, but not with attention. A recent study in asylum seekers confirmed that verbal memory deficits specifically, and not other neuropsychological deficits, are related to depressive symptoms in PTSD (Johnsen, Kanagaratnam, & Asbjørnsen, 2008). However, a meta-analysis of studies on executive function in PTSD found that divided...
attention and working memory were significantly related to the severity of comorbid depressive symptoms in PTSD populations, whereas selective attention and interference were not (Polak et al., 2012).

The purpose of the current study is to investigate neurocognitive deficits in PTSD patients with and without MDD. Knowing more about these deficits can help us understand whether PTSD and comorbid MDD are part of the same construct, as well as have potential clinical relevance regarding treatment of PTSD (Wild & Gur, 2008). Neurocognitive tests in this study were selected based on their close approximation of the everyday difficulties that patients with PTSD and MDD face. Based on the previously mentioned studies, we hypothesized that those PTSD patients with comorbid MDD would have a significantly lower performance on tests of verbal memory and executive functioning than PTSD patients without MDD.

Method

Participants

Participants included in this study were 140 outpatients who had a diagnosis of PTSD after various single traumatic events who sought treatment at the Academic Medical Center at the University of Amsterdam. They agreed to participate in a randomized clinical trial comparing the effects of two forms of trauma-focused psychotherapy. Further details about the randomized controlled trial are described elsewhere (Nijdam, Gersons, Reitsma, De Jongh & Olff, 2012). The PTSD+MDD group consisted of 84 patients who met criteria for a major depressive disorder at baseline, and the PTSD–MDD group consisted of 56 patients who did not meet the criteria for a major depressive disorder at baseline. In this article, we report on data of the first assessment, which took place before patients were randomized and received treatment.

Study inclusion criteria were: 1) a PTSD diagnosis according to DSM-IV; 2) a single traumatic event that led to the development of PTSD and had stopped at the time of inclusion; 3) age between 18 and 65 years; 4) mastery of the Dutch language. Exclusion criteria were: 1) acute suicidality; 2) current severe MDD or current severe alcohol or substance dependence according to DSM-IV; 3) a lifetime psychotic disorder according to DSM-IV; and 4) a severe personality disorder according to the SCID-II screener (First, Gibbon, Spitzer, Williams, & Benjamin, 1997) and DSM-IV (classified as severe if more than the required number of symptoms were present and the disorder persistently influenced the person in multiple areas of
functioning over a prolonged period in life). Patients with a history of earlier traumatic experiences were allowed to participate in the trial. For patients on parallel pharmacological treatment, a stable regimen for at least four weeks was required before entering the study.

**Measures**

**Clinical measures**

PTSD diagnoses were established by means of the Structured Interview for PTSD (Davidson, Malik, & Travers, 1997), which operationalizes the DSM-IV criteria for PTSD and measures their frequency and severity. MDD diagnoses and other comorbid psychiatric diagnoses were assessed with the Structured Clinical Interview for DSM-IV Disorders (SCID-I/P; Spitzer, Gibbon, Janet M, & Janet W, 1996). A Dutch version of the Impact of Event Scale–Revised (IES-R) was used as a self-report of PTSD symptom severity (Weiss & Marmar, 1997). Unlike the original revised version in which categories from 0–4 are used, this Dutch IES-R rates the frequency of each item in the preceding week as 0 (= not at all), 1 (= rarely), 3 (= sometimes), and 5 (= often) and the total PTSD score (range 0–110) consists of the sum of the scores. The depression scale of the Hospital Anxiety and Depression Scale (HADS) was used to measure the severity of the depressive symptoms by self-report (Zigmond & Snaith, 1983). All of these measures have been widely used in trauma research and have been shown to have good psychometric properties (Creamer, Bell, & Failla, 2003; Davidson et al., 1997; Spinhoven et al., 1997; Zanarini & Frankenburg, 2001).

**Neuropsychological measures**

The California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) is a multi-trial serial learning test that measures encoding, short-term retrieval, long-term retrieval, and recognition of verbal information. A grocery list of 16 items is presented five times (List A), and patients are instructed to recall as many items as possible after each presentation. The sum of correct responses on these first five trials is a measure of encoding performance (range of correct responses 0–80). After a distracting list (List B), patients are asked to recall List A at once (short-term retrieval; range 0–16) and after an interval of 20 min (long-term retrieval; range 0–16). Cued retrieval is measured by giving semantic cues to enhance recall, measured both immediately (short-term cued retrieval) and after a 20 min interval (long-term cued retrieval). Recognition memory is measured on a 44-item
The role of major depression in neurocognitive functioning in patients with posttraumatic stress disorder

Memory traces of trauma

list including items of List A and B, and unfamiliar words; patients are asked to identify whether the word was part of List A or not (range of correct responses 0–44). Psychometric properties of the CVLT are sufficient (Paolo, Tröster, & Ryan, 1997).

The Paragraph Recall Subtest of the Rivermead Behavioural Memory Test (RBMT; Wilson, Cockburn, & Baddeley, 1985) is a test of short-term and long-term verbal memory. It is a test of everyday memory consisting of two newspaper excerpts read out loud to the patient. The patient is asked to recall the excerpt directly after hearing it (short-term retrieval) and after a 15 min interval (long-term retrieval). The sum of correctly recalled items determines the test score (range 0–42). The RBMT has shown to be a valid and reliable indicator of memory impairment in various populations (Wilson, Cockburn, Baddeley, & Hiorns, 1989).

The Trail Making Test (TMT) is a test to measure shift of attention, planning and cognitive flexibility (Reitan, 1955). Patients are asked to track a number sequence on a paper sheet (Part A) and a sequence of alternating numbers and letters (Part B) as fast as possible. The required time in seconds is measured and constitutes the score on the test. The time needed to complete part A and part B are both measures of mental speed, with part B focusing more on alternated attention. Reliability and validity of the TMT is high (Lezak, 1995).

The Stroop Color Word Test is thought to measure selective attention and cognitive flexibility (Homack & Riccio, 2004). This well-known test consists of three trials. With the first card, patients are asked to read out loud colour names printed in black ink. With the second card, they are asked to name blocks of the same colours. On the third card, the colour names are printed in incongruent ink, and patients are asked to name the colour of the ink. The interference score is calculated by the time in seconds used to complete the third card, minus the time in seconds on the second card. The reliability of the Stroop Color Word Test is sufficient (Strauss, Allen, Jorgensen, & Cramer, 2005).

Procedure

At the start of the assessments, the procedure of the study was fully explained, after which patients were asked to participate and give their written informed consent. Psychologists or master’s level psychology students under the supervision of an experienced psychologist carried out assessments. Patient confidentiality was maintained. The Institutional
Medical Ethics Committee of the Academic Medical Center approved this study.

**Statistical analyses**
Analyses were conducted using SPSS version 19.0 (IBM SPSS, USA). Chi-square tests and independent t-tests were used to compare baseline demographic and clinical characteristics between the two groups. Square root and square transformations were performed if distributions significantly departed from the normal distribution curve. Square transformations were performed for the CVLT variables and square root transformations for TMT and Stroop variables. Two outliers were excluded from the analysis of CVLT variables and one outlier from the analysis of TMT and Stroop variables. Mean scores on all outcome variables per neuropsychological test were analysed in a multivariate general linear model as a function of the presence of MDD (two levels). If this overall test was significant, we examined group differences on the separate test variables within the univariate general linear model. Two-tailed tests were applied throughout and level of significance was set at $\alpha=0.05$ for the multivariate tests. Level of significance for the univariate analyses was set at $\alpha=0.01$ to correct for multiple testing. Partial-eta squared was calculated as an effect size for significant differences.

**Results**

**Demographic and clinical characteristics**
Demographic and clinical characteristics of the two groups are displayed in Table 1. No significant differences emerged on demographic variables or clinical features between the PTSD+MDD and PTSD–MDD groups, except that the PTSD+MDD group had significantly more severe PTSD symptoms on the IES-R and significantly more severe depressive symptoms on the HADS than the PTSD–MDD group (Table 1).
Chapter 2

The role of major depression in neurocognitive functioning in patients with posttraumatic stress disorder

Table 1. Demographic and clinical characteristics of the PTSD+MDD and PTSD-MDD group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PTSD+MDD (n=84)</th>
<th>PTSD-MDD (n=56)</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Female</td>
<td>50</td>
<td>59.5</td>
<td>29</td>
</tr>
<tr>
<td>Education</td>
<td>1.53</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Low</td>
<td>19</td>
<td>22.6</td>
<td>12</td>
</tr>
<tr>
<td>Middle</td>
<td>43</td>
<td>51.2</td>
<td>24</td>
</tr>
<tr>
<td>High</td>
<td>22</td>
<td>26.2</td>
<td>20</td>
</tr>
<tr>
<td>Dutch</td>
<td>40</td>
<td>47.6</td>
<td>33</td>
</tr>
<tr>
<td>Type of trauma</td>
<td>6.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assault</td>
<td>39</td>
<td>46.4</td>
<td>35</td>
</tr>
<tr>
<td>Sexual assault</td>
<td>11</td>
<td>13.1</td>
<td>5</td>
</tr>
<tr>
<td>Accident</td>
<td>20</td>
<td>23.8</td>
<td>6</td>
</tr>
<tr>
<td>Disaster</td>
<td>5</td>
<td>6.0</td>
<td>5</td>
</tr>
<tr>
<td>War-related</td>
<td>4</td>
<td>4.8</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>6.0</td>
<td>2</td>
</tr>
<tr>
<td>Earlier traumatic experiences</td>
<td>48</td>
<td>57.1</td>
<td>28</td>
</tr>
<tr>
<td>Anxiety disorder other than PTSD (SCID-I)</td>
<td>13</td>
<td>15.5</td>
<td>9</td>
</tr>
<tr>
<td>Lifetime alcohol related disorder (SCID-I)</td>
<td>3</td>
<td>3.6</td>
<td>1</td>
</tr>
<tr>
<td>Lifetime substance related disorder (SCID-I)</td>
<td>2</td>
<td>2.4</td>
<td>3</td>
</tr>
<tr>
<td>On psychoactive medication</td>
<td>39</td>
<td>46.4</td>
<td>20</td>
</tr>
<tr>
<td>On SSRI</td>
<td>18</td>
<td>21.4</td>
<td>7</td>
</tr>
<tr>
<td>Age</td>
<td>Mean S.D.</td>
<td>37.32</td>
<td>11.26</td>
</tr>
<tr>
<td>Time since trauma (months)</td>
<td>Mean S.D.</td>
<td>25.17</td>
<td>44.99</td>
</tr>
<tr>
<td>PTSD total score (IES-R)</td>
<td>Mean S.D.</td>
<td>81.98</td>
<td>16.61</td>
</tr>
<tr>
<td>Depression severity score (HADS)</td>
<td>Mean S.D.</td>
<td>13.20</td>
<td>3.85</td>
</tr>
</tbody>
</table>

SCID-I, Structured Clinical Interview for DSM-IV Disorders; PTSD, posttraumatic stress disorder; MDD, major depressive disorder; SSRI, selective serotonin reuptake inhibitor; IES-R, Impact of Event Scale–Revised; HADS, Hospital Anxiety and Depression Scale.

*Fisher’s exact test.

Neurocognitive performance

Mean scores and standard deviations of the two groups on the neurocognitive tests are displayed in Table 2. The multivariate F-test revealed a significant difference between the groups for the CVLT,
Chapter 2

The role of major depression in neurocognitive functioning in patients with posttraumatic stress disorder

Univariate analyses revealed that the PTSD+MDD group scored significantly lower on CVLT sum of trials 1–5, $F(1,135)=8.63$, $p=0.004$, $\eta^2=0.058$; CVLT short-term cued recall, $F(1,135)=8.15$, $p=0.005$, $\eta^2=0.057$; CVLT long-term free recall, $F(1,135)=10.98$, $p=0.001$, $\eta^2=0.069$; and CVLT long-term cued recall, $F(1,135)=7.77$, $p=0.006$, $\eta^2=0.053$, than the PTSD–MDD group. Multivariate $F$-tests did not reveal significant differences between the groups for the RBMT, $F(2,136)=2.90$, $p=0.059$; TMT, $F(2,135)=1.10$, $p=0.337$; or Stroop, $F(3,134)=1.88$, $p=0.137$.

**Table 2.** Means and standard deviations on neurocognitive measures for PTSD+MDD and PTSD-MDD groups

<table>
<thead>
<tr>
<th>Measure</th>
<th>PTSD+MDD ($n=83$)</th>
<th>PTSD-MDD ($n=56$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>S.D.</td>
</tr>
<tr>
<td>CVLT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sum of trials 1-5</td>
<td>47.3</td>
<td>10.8</td>
</tr>
<tr>
<td>Short-term free recall</td>
<td>10.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Short-term cued recall</td>
<td>11.3</td>
<td>2.7</td>
</tr>
<tr>
<td>Long-term free recall</td>
<td>10.7</td>
<td>3.1</td>
</tr>
<tr>
<td>Long-term cued recall</td>
<td>11.6</td>
<td>2.8</td>
</tr>
<tr>
<td>Long-term recognition</td>
<td>41.3</td>
<td>3.0</td>
</tr>
<tr>
<td>RBMT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall</td>
<td>15.2</td>
<td>6.0</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>11.4</td>
<td>5.6</td>
</tr>
<tr>
<td>TMT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail A</td>
<td>37.5</td>
<td>23.1</td>
</tr>
<tr>
<td>Trail B</td>
<td>88.8</td>
<td>40.4</td>
</tr>
<tr>
<td>Stroop</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Card 2</td>
<td>69.6</td>
<td>24.8</td>
</tr>
<tr>
<td>Card 3</td>
<td>115.8</td>
<td>66.2</td>
</tr>
<tr>
<td>Interference</td>
<td>46.3</td>
<td>45.6</td>
</tr>
</tbody>
</table>

PTSD, posttraumatic stress disorder; MDD, major depressive disorder; CVLT, California Verbal Learning Test; RBMT, Rivermead Behavioural Memory Test; TMT, Trail Making Test.

*One participant did not complete the neuropsychological assessment at baseline.

*A significant overall group difference was found for the CVLT, $p=0.011$, as well as group differences for CVLT sum of trials 1-5, $p=0.004$, CVLT short-term cued recall, $p=0.005$, CVLT long-term free recall, $p=0.001$, and CVLT long-term cued recall, $p=0.006$.

**Discussion**

The main finding of the current study is that treatment-seeking patients with PTSD and comorbid MDD have more pronounced verbal memory deficits than patients with PTSD alone, with medium-sized differences.

Memory traces of trauma
between the groups. These verbal memory deficits in the group with PTSD and MDD seem to be restricted to the encoding, short-term retrieval and long-term retrieval of separate words, since there were no significant differences in retrieval of a coherent paragraph or in recognition between the two groups. Various aspects of executive functioning in the present study were similar for both groups as well, as expressed by a lack of differences on measures of mental speed, shift of attention, selective attention, and cognitive interference. In sum, encoding and retrieval of separate words was a bigger challenge for PTSD patients who had comorbid MDD diagnoses, than for those who had PTSD without MDD. Results of this study thus suggest a somewhat more impaired neurocognitive profile for PTSD patients with comorbid MDD.

Our results confirm and extend the studies of Sachinvala et al. (2000) and Johnsen et al. (2008), which found verbal memory deficits, but not other neurocognitive performance, to be related to the severity of depressive symptoms in various PTSD populations. The results of the current study partly agree with the meta-analytic findings of Polak et al. (2012), who found that comorbid depressive symptoms were not related to selective attention and interference in PTSD populations. However, we found no evidence of an association between comorbid depressive symptoms and shift of attention as found by this meta-analysis. The results of our study are also in contrast with the neuropsychological disturbances found in MDD patients, which are most clear in the domain of mental flexibility and control (Veiel, 1997). Possibly, a combination of PTSD and comorbid MDD leads to a different neurocognitive profile than a diagnosis of MDD alone.

We note that the group with PTSD and comorbid MDD in our study also had more severe PTSD symptoms than the group without comorbid MDD. Therefore, it is possible that the differences we found between the groups are partly attributable to greater PTSD symptom severity. Moreover, it could be the case that PTSD symptom severity contributes to the other neuropsychological processes (e.g., retrieval of a coherent paragraph, shifting of attention, cognitive interference) for which we were not able to confirm statistically significant group differences. However, more severe PTSD symptoms and a comorbid MDD diagnosis are such intertwined constructs that it is very difficult, and may not even be clinically meaningful, to statistically separate the influence of these two variables (Miller & Chapman, 2001). Even though one may discuss whether this is clinically meaningful, inserting PTSD symptom severity as a covariate in our analyses...
still yielded significant differences on verbal memory between PTSD patients with and without MDD.

Limitations of this study include that we did not administer tests for all types of attention and that we had to exclude patients with severe MDD, as this was an exclusion criterion for the treatment trial. It would be interesting to examine especially sustained attention in samples with PTSD+MDD versus PTSD alone, as depressive symptoms were also found to play a role in sustained attention in PTSD (Meewisse et al., 2005). As our sample consisted of PTSD patients seeking help for single traumatic events, results are not necessarily representative for other PTSD populations. Though more than half of the patients in the current study had experienced multiple traumatic events or early life trauma besides the single traumatic event for which they sought help, results may not extrapolate to survivors with PTSD and MDD resulting from more chronic traumatic experiences. Replication and extension of the neuropsychological findings of the current study is therefore much encouraged, preferably also in trauma survivors who developed MDD on its own after traumatic experiences. It would also be interesting to explore the link between PTSD, MDD, and neuropsychology by investigating associations between neurocognitive impairment and specific PTSD symptoms that do or do not overlap with comorbid MDD (Brewin et al., 2007).

In conclusion, patients with PTSD and comorbid MDD seem to have more difficulty in learning separate units of verbal information and retrieving this information in the short and long term than PTSD patients without comorbid MDD, even when the severity of the MDD diagnosis is only mild to moderate. PTSD symptom severity may contribute to these difficulties. From a clinical standpoint, it is good to be aware that these aspects of verbal memory are more restricted in patients with comorbid PTSD and MDD, as verbal memory performance can influence the treatment outcome of trauma-focused psychotherapy (Wild & Gur, 2008; Nijdam, De Vries, Gersons & Olff, submitted). The clinical relevance of the differences we found between PTSD patients with and without MDD, with medium effect sizes, requires further study. These neuropsychological deficits may help us to determine subgroups of PTSD patients with different treatment prognoses and in the future possibly more targeted interventions.

References


Nijdam, M. J., Gersons, B. P. R., Reitsma, J. B., De Jongh, A., & Olff, M. (2012). Brief eclectic psychotherapy v. eye movement desensitisation and reprocessing therapy in the treatment of post-
Chapter 2

The role of major depression in neurocognitive functioning in patients with posttraumatic stress disorder


Disaster-related posttraumatic stress symptoms and sustained attention: evaluation of depressive symptomatology and sleep disturbances as mediators.

Abstract
Research about attentional functioning following trauma has almost exclusively been performed in patient populations with combat-related posttraumatic stress disorder (PTSD). In this study the relationship between sustained attention and PTSD symptoms was examined in a community sample of survivors of a major disaster using the Paced Auditory Serial Addition Task (PASAT) and the Self-Rating Scale for PTSD (SRS-PTSD) 2–3 years postdisaster. Analyses revealed low but significant partial correlations between PTSD symptoms and the least difficult subtests, ruling out the effects of age, education, depressive symptomatology, and sleep disturbances. These results demonstrate that PTSD symptoms link to attentional dysfunction 2–3 years postdisaster.
Introduction

Studies investigating attention in survivors of traumatic events with posttraumatic stress disorder (PTSD) have almost exclusively focused on treatment-seeking patients with combat-related trauma. Although these studies have produced mixed results, many report attentional deficits in PTSD (e.g., Gilbertson, Gurvits, Lasko, Orr, & Pitman, 2001; Sachinvala et al., 2000; Vasterling et al., 2002). Deficits in sustained attention, which cause difficulties in executing a long-lasting task, were found most frequently.

Characteristics of the participants in the above-mentioned studies include high symptom severity and coexisting psychopathology, especially substance abuse disorders. Likely, these studies may represent populations that could differ from community samples in important ways. Therefore, the purpose of the present study was to investigate sustained attention in relation to PTSD symptom severity in a community sample of inhabitants of an area afflicted by a major disaster. To our knowledge, this is the first study of attention in such a unique population. After a traumatic event, the most frequently developed disorders are major depressive disorder (MDD) and PTSD. Symptoms of these disorders overlap and high comorbidity up to 40% is reported. Knowing that both disorders are characterized by symptoms of impaired attention (DSM-IV; American Psychiatric Association, 1994), we raise the question whether this symptom is independent of depressive symptoms in PTSD. Therefore, we investigated whether attention in survivors is still related to PTSD symptom severity when we control for the influence of depressive symptoms. Furthermore, to assure that worsened attentional performance is not the consequence of sleep disturbances, we also examined the effect of sleep disturbances in the relationship between PTSD symptoms and attention. We expected to find negative relationships between PTSD symptom severity and attentional performance, even when controlling for the effects of depressive symptoms and sleep disturbances.

Method

Participants

Participants were survivors of the fireworks disaster in the city of Enschede, The Netherlands, on May 13, 2000. The explosion of a fireworks storage depot completely destroyed the surrounding residential district. Twenty-two people were killed outright and almost one thousand were
injured. Over 10,000 local residents were evacuated for one or more days, while over 1,200 people lost their homes completely (Roorda, Van Stiphout, & Huijsman-Rubingh, 2004). Participants of the present study were Dutch-speaking adults, over 19 years of age, living in the affected area at the time of the disaster. They were a sample of participants in a large prospective study monitoring health \( (n = 1,567) \) after the disaster (Kamp & Van der Velden, 2001) and agreed to participate in neuropsychological testing as a two-year follow-up to their initial participation. For the main study, inhabitants of the disaster area were invited by a letter of the Dutch Ministry of Health Welfare and Sports to participate within 2 to 3 weeks postdisaster. In addition, announcements for the study were made in the media.

**Measures**

**Symptom Severity Measures**

To determine the severity of PTSD and MDD symptoms, participants completed two self-report measures. The Self-Rating Scale for PTSD (SRS-PTSD; Carlier, Lamberts, Van Uchelen, & Gersons, 1998) was administered to obtain a severity score for PTSD symptoms based on *DSM-IV* criteria. Participants were asked specifically to consider the fireworks disaster when completing this measure. The internal consistency and interjudge reliability of this self-report are found to be satisfactory. The Dutch version of the Symptom Check List-90 (SCL-90; Arrindell & Ettema, 1986) was administered to measure the severity of depressive symptoms (16 items) and sleep disturbances (3 items). These items are scored on a 5-point Likert scale. The internal consistency of the test is good, and both the construct and the predictive validity are adequate.

**Measure of Attention**

To assess impairments in divided and sustained attention and speed of processing, the Dutch version of the Paced Auditory SerialAddition Task (PASAT; Aarnoudse, Van den Burg, & Saan, 1995; Gronwall, 1977) was used. The objective of this test is to add 60 pairs of randomized digits in the range of 1 to 6, which are presented at 5 rates of speed with 3.2, 2.8, 2.4, 2.0, and 1.6 seconds between successive digits on an audiotape. The PASAT has shown high convergent validity and modest discriminant validity, because of its relationship to general intelligence (Deary, Langan, Hepburn, & Frier, 1991). Furthermore, PASAT performance is significantly correlated with age.
and education (Brittain, La Marche, Reeder, Roth, & Boll, 1991). Aarnoudse et al. (1995) found high reliabilities for the Dutch version.

**Procedure**

Self-report measures for the main study were completed at 2 to 3 weeks postdisaster. Between 23 and 38 months ($M = 2.1$ years, $SD = 0.2$) postdisaster, self-report measures were repeated and the attention test was administered for the present study. Prior to this participation, brochures with extensive information were sent to participants of the main study and upon agreement an appointment was set for the PASAT to be administered by trained research employees. The study protocol was approved by the Medical Ethics Committee of the Academic Medical Center, Amsterdam, The Netherlands, and participants gave written informed consent.

**Statistical Analyses**

Chi-square tests and independent $t$ tests were used to examine whether survivor groups in this follow-up differed in terms of socio-demographic features and symptom severity from survivors of the main study at 2 to 3 weeks postdisaster. Relationships between PTSD symptom severity and PASAT performance were analyzed using partial correlations, successively controlling for age, years of education, depressive symptoms, and sleep disturbances. All statistical tests were two-tailed, and $p$ values of less than .05 were considered statistically significant.

**Results**

Attentional testing and symptom severity measures were completed by 124 participants with an average age of 45.6 years ($SD = 14.1$), 64.5% were of the female gender, the mean number of years of education was 13.3 ($SD = 3.9$), and 66.1% were employed. The mean SRSPTSD was 5.7 ($SD = 4.2$) and the mean scores for SCL-90 depressive symptoms and sleep disturbances were 25.7 ($SD = 11.0$) and 5.9 ($SD = 3.2$).

When we compared the subgroup of survivors included in the present study to other participants in the main study on measures collected 2 to 3 weeks postdisaster, no differences in terms of age, employment, or sickness-leave from work were apparent. However, we did find a between-group difference for gender: $\chi^2(1, N = 1566) = 6.91, p < .05$, and for years of education $t(153.74) = 2.67, p < .05$. A higher proportion of women and higher-educated persons participated in this part of the study. No
Chapter 3

Disaster-related posttraumatic stress symptoms and sustained attention: evaluation of depressive symptomatology and sleep disturbances as mediators

differences in PTSD symptoms, depressive symptoms, or sleep disturbances were found between the groups.

The nature of the participants’ exposure consisted in part of being severely frightened (66.7%), running away from home (44.1%) or into their homes (18.0%), seeing slightly (72.1%) and severely (27.9%) wounded victims, helping the wounded (9.0%), searching for loved ones (56.7%), having seen explosions (80.2%) or fire (58.6%), and having heavy damage or total destruction of one’s house (23.1%).

Results of the partial correlations between the number of correct responses on each presentation rate of the PASAT and the SRS-PTSD, controlling successively for age, education, depressive symptoms, and sleep disturbances can be seen in Table 1.

Results indicate that PASAT performance decreases with increasing PTSD symptom severity. When we inserted the controlling variables the correlations lowered; the statistical significance disappears when the task gets more difficult.

Table 1. Partial correlation coefficients of PTSD symptom severity (SRS-PTSD) and PASAT scores controlling successively for age, education, depressive symptoms (SCL-90), and sleep disturbances (SCL-90).

<table>
<thead>
<tr>
<th>Controlling variables</th>
<th>PASAT 3.2-sec</th>
<th>PASAT 2.8-sec</th>
<th>PASAT 2.4-sec</th>
<th>PASAT 2.0-sec</th>
<th>PASAT 1.6-sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>-.30**</td>
<td>-.28**</td>
<td>-.25**</td>
<td>-.21*</td>
<td>-.08</td>
</tr>
<tr>
<td>Age, education</td>
<td>-.19*</td>
<td>-.21*</td>
<td>-.19*</td>
<td>-.09</td>
<td>-.02</td>
</tr>
<tr>
<td>Age, education, depression</td>
<td>-.20*</td>
<td>-.25*</td>
<td>-.16</td>
<td>-.13</td>
<td>-.08</td>
</tr>
<tr>
<td>Age, education, depression, sleep disturbances</td>
<td>-.20*</td>
<td>-.23*</td>
<td>-.13</td>
<td>-.15</td>
<td>-.06</td>
</tr>
</tbody>
</table>

Note. PTSD = posttraumatic stress disorder; SRS-PTSD = Self-Rating Scale for PTSD; PASAT = Paced Auditory Serial Addition Task; SCL-90 = Symptom Checklist. Because of missing data, sample sizes for the correlations vary.

Using Pearson correlation.
*p < .05. **p < .01.

Discussion

To our knowledge, this is the first study to investigate attention in disaster survivors in relation to PTSD symptomatology at 2 to 3 years postdisaster. Participants stem from a community population and are survivors of the Enschede fireworks disaster. As expected, age and education accounted for a great deal of attentional dysfunction in disaster survivors, and although
depressive symptoms and sleep disturbances contributed as well, these concomitant symptoms to PTSD explained only a very small part of the difficulties. Nevertheless, the current findings suggest that even when we controlled for the influence of age, education, depressive symptoms, and sleep disturbances, attentional dysfunction is still related to PTSD symptoms.

Our results are consistent with the study of Jenkins, Langlais, Delis, and Cohen (2000) who found that depressive symptomatology plays only a minor role in mediating deficits in sustained attention in PTSD sufferers. In studies in which no attentional disturbances in PTSD were found (e.g., Sullivan, Krengel, Proctor, Devine, Heeren et al., 2003; Zalewski, Thompson, & Gottesman, 1994), it is conceivable that these contrasting results can be attributed to partial or subclinical PTSD in the traumatized controls who were used as a comparison group. In this way, small differences in PTSD symptom severity could be the cause of not detecting any attentional deficits.

We recognize the limitations of our study. Our sample may not be representative for survivors of other disasters. Therefore, generalizing the results to different populations should be done with caution. Second, because our interpretations are based on only one measure of attention, replication is necessary, preferably with several neuropsychological tests.

Attention lies at the basis of all adequate information processing. As such, attention is an important prerequisite for adequate functioning in work and daily life. Stein, Kennedy, and Twamley (2002) stated that even mild or subtle impairments on neuropsychological tests in the laboratory can translate into clinically significant difficulties in the real world, because real world situations involve more complex processing demands in the context of increased distraction in the environment. Moreover, small individual attentional impairments may have an important negative impact on the total population.

In conclusion, this study provides further evidence that PTSD symptoms are genuinely related to deficits in attention. Early screening and subsequent adequate treatment of PTSD symptoms in the community are needed to prevent these attentional constraints from causing populations to fall behind in the aftermath of trauma.

References
addition task (PASAT) in een steekproef van gezonde personen: betrouwbaarheden en normeringen [The Paced Auditory Serial Addition Task (PASAT) in a sample of healthy individuals: Reliabilities and norms]. Groningen: Afdeling neuropsychologie, Academisch Ziekenhuis Groningen.


Chapter 3
Disaster-related posttraumatic stress symptoms and sustained attention: evaluation of depressive symptomatology and sleep disturbances as mediators


Chapter 4


Abstract

Background: Trauma-focused cognitive–behavioural therapy (CBT) and eye movement desensitisation and reprocessing therapy (EMDR) are efficacious treatments for post-traumatic stress disorder (PTSD), but few studies have directly compared them using well-powered designs and few have investigated response patterns.

Aims: To compare the efficacy and response pattern of a trauma-focused CBT modality, brief eclectic psychotherapy for PTSD, with EMDR (trial registration: ISRCTN64872147).

Method: Out-patients with PTSD were randomly assigned to brief eclectic psychotherapy (n = 70) or EMDR (n = 70) and assessed at all sessions on self-reported PTSD (Impact of Event Scale – Revised). Other outcomes were clinician-rated PTSD, anxiety and depression.

Results: Both treatments were equally effective in reducing PTSD symptom severity, but the response pattern indicated that EMDR led to a significantly sharper decline in PTSD symptoms than brief eclectic psychotherapy, with similar drop-out rates (EMDR: n = 20 (29%), brief eclectic psychotherapy: n = 25 (36%)). Other outcome measures confirmed this pattern of results.

Conclusions: Although both treatments are effective, EMDR results in a faster recovery compared with the more gradual improvement with brief eclectic psychotherapy.
Chapter 4


**Introduction**

After experiencing an event in which one’s life is in imminent danger and one feels completely helpless, the conditional risk for developing post-traumatic stress disorder (PTSD) is 9–14% (Breslau et al., 1998; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; De Vries & Olff, 2009). Two trauma-focused psychotherapy methods, trauma-focused cognitive–behavioural therapy (CBT) and eye movement desensitisation and reprocessing therapy (EMDR), are the most efficacious psychological treatments for PTSD currently available. Their effect sizes have proven to be equally large (NICE, 2005; Foa, Keane, Friedman, & Cohen, 1998; Seidler & Wagner, 2006), and there are some indications that EMDR leads to faster recovery (Ironson, Freund, Strauss, & Williams, 2002). However, no studies have compared these treatments directly in sufficiently powered designs, and few studies have investigated the response pattern. The PTSD guideline of the National Institute for Health and Clinical Excellence (NICE, 2005) has also emphasised that adequately powered randomised trials should be conducted to compare these treatments, and to provide information about their value in clinical practice. Therefore, our aim was to conduct a well-powered randomised trial comparing the efficacy of, and response patterns to, treatment with EMDR and brief eclectic psychotherapy for patients with PTSD resulting from various types of psychological trauma. Brief eclectic psychotherapy was originally developed in The Netherlands and classified as a trauma-focused CBT in accordance with the NICE guideline (NICE, 2005). Although it includes some elements of other therapeutic schools, its main treatment components overlap with those of other trauma-focused CBT interventions. Some elements of ‘practical trials’ (trials that include elements of effectiveness designs) were included in the current trial to increase the extent to which results can be generalised to routine clinical practice and inform healthcare decisions (Schnurr, 2007). In line with a previous pilot study (Ironson et al., 2007), we hypothesised that EMDR would lead to faster improvements in PTSD symptomatology than brief eclectic psychotherapy and that the improvements at the end would be equal. Trial registration: Dutch Trial Register, number NTR46 and ISRCTN64872147.
Chapter 4


Method

Participants were recruited from the Centre for Psychological Trauma of the Academic Medical Centre in Amsterdam, The Netherlands, between December 2003 and January 2009 following ethics committee approval. Participants were civilian trauma survivors, who were referred to our centre by general practitioners, victim support workers, occupational physicians and other Academic Medical Centre departments. If a PTSD diagnosis was presumed at intake, individuals were approached for the study. After potential participants received a complete description of the study, written informed consent was obtained.

Study entry criteria

Study entry criteria were: a PTSD diagnosis according to DSM-IV (APA, 1994); a single traumatic event (which had stopped at the time of inclusion) that led to the development of PTSD; age between 18 and 65 years; and mastery of the Dutch language. Exclusion criteria were: acute suicidality; current severe major depressive disorder or current severe alcohol or substance dependence according to DSM-IV (patients were allowed to enter after initial treatment of these disorders); lifetime psychotic disorder according to DSM-IV; and severe personality disorder according to the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II; First, Gibbon, Spitzer, Williams, & Benjamin, 1997) and DSM-IV. Patients with a history of earlier traumatic events were allowed to participate in the trial. Prior to entering the trial, patients who were on parallel pharmacological treatment were required to be on a stable medication dose for at least 4 weeks, and patients with prior alcohol or substance dependence were required to be abstinent for at least 3 months. During treatment, medication dosage was maintained as much as possible, but in agreement with clinical guidelines patients were allowed to stop anxiolytic medication to better engage in trauma processing. Participants were not allowed to attend any other trauma-focused intervention during their treatment in the trial.

Design

The study was a randomised controlled trial in which brief eclectic psychotherapy was compared with EMDR. The choice of brief eclectic psychotherapy, instead of another trauma-focused CBT intervention, was made because it explicitly combines the most effective ingredients of trauma-focused CBT such as psychoeducation, imaginal exposure, cognitive...

restructuring and writing assignments. Its effect sizes in previous studies with similar populations (Lindauer et al., 2005; Olff, De Vries, Güzelcan, Assies, & Gersons, 2007) are equal to those of other trauma-focused cognitive–behavioural interventions (Bradley, Greene, Dutra, Russ, & Westen, 2005).

Participants were randomised to brief eclectic psychotherapy or EMDR in a parallel design. Random assignment was done on a 1:1 basis by a computer program, with a weighted maximum of subscribing four times the same treatment in a row. To ensure masking of assessors, one psychologist who had no other engagement in the study, had access to the computer program, kept a log file of all random assignments and assigned the patients to the therapists.

Both EMDR and brief eclectic psychotherapy were carried out according to treatment manuals and administered as in clinical practice, allowing for the number of sessions to vary depending on recovery. Leading trainers and supervisors in brief eclectic psychotherapy (B.P.R.G.) and EMDR (A.d.J.) were included in the study to control for an investigator allegiance effect. The primary outcome measure for self-reported PTSD symptoms was the Impact of Event Scale – Revised (IES-R; Weiss & Marmar, 1997), which was administered at baseline and at every weekly treatment session, as well as during a final assessment at week 17 when treatments had finished. Secondary outcomes were clinician-rated PTSD, depressive and general anxiety symptoms, which were also assessed at baseline and at week 17 (i.e. second post-assessment). Brief eclectic psychotherapy differs from EMDR in treatment duration and consists of two phases. Therefore, at mid-term an additional assessment was scheduled (first post-assessment) that was conducted after the EMDR treatment (mean 6.5 sessions) and after the first phase of brief eclectic psychotherapy (6 sessions; Fig. 1).
Figure 1. Study design and patients’ flow throughout trial.
PTSD, post-traumatic stress disorder. a. Number of sessions refers to the sessions completed by the participants. b. Patients who prematurely dropped out of
Chapter 4


treatment ($n = 32$) were contacted and the following reasons for drop-out were given: patient did not notice any improvement ($n = 8$), patient felt no further need to continue therapy ($n = 3$), patient experienced a new trauma or recurring threat ($n = 3$), patient wanted a different focus in treatment ($n = 2$), unknown because patient could not be located ($n = 16$). c. Patients who did not receive any treatment ($n = 13$) had health problems ($n = 3$) or withdrew from treatment before the first session ($n = 10$).

Interventions

The therapists were psychiatry residents or master’s level clinical psychologists, who received a 3-day level-I training for EMDR and for brief eclectic psychotherapy. Prior experience with PTSD treatment was not required. A total of 38 therapists delivered the treatments; of these 7 delivered both. They received biweekly group supervision. All sessions were audiotaped. Treatment adherence protocols were developed to rate six brief eclectic psychotherapy sessions (session 1, 2, 4, 11, 13 and 15) and three EMDR sessions (first, second and second to last). Treatment adherence coding systems were based on a previous brief eclectic psychotherapy study (Lindauer et al., 2005) and an EMDR Fidelity Scale (Korn, Zangwill, Lipke, & Smyth, 2001) adapted for use with the Dutch EMDR protocol.

Eye movement desensitisation and reprocessing

The weekly EMDR sessions lasted 90 min and were applied according to the Dutch treatment manual (De Jongh & Ten Broeke, 2004). During EMDR therapy, the most distressing images of the traumatic event are identified and processed consecutively. After the patient has focused on an image with the corresponding negative cognition, the most distressing emotion and the bodily location of the emotion, the patient is continuously asked to follow the therapist’s finger making saccadic movements in alternation with the patient’s own associations. Current distress is rated every 5–10 min, until the distress level is 0 or 1, after which a more positive cognition is introduced in relation to the target image. This procedure is repeated for the other distressing images and treatment sessions are terminated when the trauma memory feels neutral. Auditory bilateral stimulation was used if problems with eye movements were encountered (such as if they induced headaches).
Chapter 4


Brief eclectic psychotherapy

Brief eclectic psychotherapy was applied according to a detailed manual (Gersons, Carlier, & Olff, 2004) and consisted of weekly sessions of 45–60 min as administered in previous studies (Lindauer et al., 2005; Olff et al., 2007; Gersons, Carlier, Lamberts, & van der Kolk, 2000). The treatment was initially developed and applied in The Netherlands and 400 therapists have been trained in this country in the last decade. Its main treatment components are also used in other trauma-focused CBT, such as psychoeducation, imaginal exposure, writing assignments and cognitive restructuring. Two main phases can be clearly distinguished; from session 2 to 6 imaginal exposure takes place, whereas sessions 7–15 are dedicated to cognitive restructuring. Session 1 consists of psychoeducation and session 16 of a farewell ritual. Some of the elements in the second phase can also be understood from other therapeutic perspectives, including grief therapy, directive therapy and a psychodynamic approach. These elements include taking mementos to the treatment session (objects that are linked to the traumatic event, such as the clothes that the person was wearing at that time, to stimulate the imaginal exposure), performing a farewell ritual that is intended to symbolically leave the trauma behind, and giving meaning to the traumatic event. The exposure in brief eclectic psychotherapy is very detailed, using sensory memories to stimulate reliving and focusing on experiencing grief. The aim is to relive the whole traumatic event in detail – in parts, over several sessions.

Measures

Assessments were conducted by trained, independent, masked assessors who were master’s level clinical psychologists or master’s level psychology students supervised by an experienced clinical psychologist. To ensure comparability among assessors, biweekly supervision took place. Before all post-assessments, patients were instructed to avoid mentioning details about the content or length of their treatment to ensure masking.

The primary outcome measure for PTSD symptom severity was the IES-R (Weiss & Marmar, 1997). Unlike the original revised version in which categories from zero to four are used, the Dutch IES-R rates the frequency of each item in the preceding week as zero (not at all), one (rarely), three (sometimes) and five (often). Clinical PTSD diagnoses were established by means of the Structured Interview for PTSD (SI-PTSD; Davidson, Malik, & Travers, 1997), which operationalises the DSM-IV criteria for PTSD. To assess comorbid psychiatric diagnoses, the Dutch version of the Structured
Chapter 4


Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was administered (Spitzer, Gibbon, Janet, & Janet, 1996; Van Groenestein, Akkerhuis, Kupka, Schneider, & Nolen, 1999). The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) was used to measure the severity of the general anxiety and depressive symptoms by self-report. All these measures have been widely used in trauma research and have been shown to have strong psychometric properties (Creamer, Bell, & Falla, 2003; Carlier, Lamberts, Van Uchelen, & Gersons, 1998; Zanarini & Frankenburg, 2001; Spinhoven et al., 1997).

**Data analysis**

Power calculations were based on post-treatment means and standard deviations of a previous study (Olff et al., 2007), which found a mean IES-R score of 49.5 (s.d. = 14.1) after brief eclectic psychotherapy for PTSD. Based on this previous study, we considered eight points on the IES-R a clinically relevant difference between the treatment conditions at post-assessment. For an equivalence design, a sample size of 47 patients per arm was needed (power 80% and two-sided significance level 0.05) to detect medium-sized treatment effects, taking into account a difference of less than eight points (δ) between the post-treatment means for equivalence of the two arms. Sample size per arm was set at 70 to allow for patient attrition of 30%.

Chi-squared tests and independent t-tests were used to compare demographic and clinical characteristics between the treatment groups. Repeated measurement analyses were used to study changes over time between the treatment groups. We applied mixed linear models to take into account that measurements within the same individual are correlated, and to allow the model to calculate estimates when data were missing at certain assessments. An auto-regressive pattern was imposed on the covariance structure for measurements within the same individual (AR1). Mean scores for each outcome at the post-measurements (17 for IES-R and 2 for SI-PTSD and HADS) were modelled as a function of the intervention given (two levels), time since intervention (as a categorical variable with 17 or 2 levels), the baseline measurement (continuous), and the interaction between time and intervention. The main question, whether the response pattern was different between the treatment conditions, was evaluated by jointly testing whether the treatment difference was zero at all post-measurements. If the overall test was significant, we examined the size of the treatment effect by calculating the difference in mean scores between the treatment conditions at separate time points, with corresponding 95%
confidence intervals in the linear mixed model. All analyses were carried out on an intent-to-treat basis, unless indicated otherwise. \( P \)-values of less than 0.05 were considered statistically significant and two-tailed tests were used throughout.

**Results**

**Participants**

Figure 1 shows the patient flow through the trial. Completer and drop-out rates did not significantly differ across treatment conditions (\( \chi^2 = 1.08, \) d.f. = 2, \( P = 0.58 \)). Table 1 displays the baseline and clinical characteristics of the two groups. No significant differences were found in clinical or demographic variables between the groups at baseline, except that the IES-R total score was significantly higher in the brief eclectic psychotherapy group than in the EMDR group (Table 1). Proportions of patients on psychoactive medication did not differ between treatment groups (Table 1). Over the 17 weeks of the trial, proportions of patients who changed psychoactive medication (\( n = 28 \)) did not significantly differ between treatment conditions (\( \chi^2 = 0.01, \) d.f. = 1, \( P = 0.91 \)). Medication changes in most cases consisted of reduction or cessation of anxiolytics and these were also equally distributed across treatment conditions (\( \chi^2 = 1.73, \) d.f. = 1, \( P = 0.18 \)). Proportions of patients attending concurrent alternative treatments over the course of the trial did not significantly differ between treatment conditions (\( \chi^2 = 1.54, \) d.f. = 1, \( P = 0.21 \)). Alternative treatments consisted of physiotherapy (\( n = 17 \)), alternative medicine (\( n = 15 \)), supportive therapy (\( n = 10 \)) and self-help groups (\( n = 1 \)). Referrals at end of treatment (\( n = 18 \)) were equally distributed across treatment conditions (\( \chi^2 = 0.00, \) d.f. = 1, \( P = 1.00 \)).
Table 1. Demographic and clinical characteristics at baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Brief Eclectic Psychotherapy group (n=70)</th>
<th>EMDR group (n=70)</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years: mean (s.d.)</td>
<td>37.3 (10.6)</td>
<td>38.3 (12.2)</td>
<td>X² 0.50, t-test 1.42, d.f. 138, P 0.62</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>43 (61.4)</td>
<td>36 (51.4)</td>
<td>2.35, 2, 0.32</td>
</tr>
<tr>
<td>Education, n (%)</td>
<td>Low 14 (20.0)</td>
<td>17 (24.3)</td>
<td>0.76, 4, 0.94</td>
</tr>
<tr>
<td></td>
<td>Middle 38 (54.0)</td>
<td>29 (41.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High 18 (25.7)</td>
<td>24 (34.0)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td>Dutch 37 (52.9)</td>
<td>36 (51.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surinamese 10 (14.3)</td>
<td>8 (11.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Turkish 7 (10.0)</td>
<td>6 (8.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moroccan 4 (5.7)</td>
<td>5 (7.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other 12 (17.1)</td>
<td>15 (21.4)</td>
<td></td>
</tr>
<tr>
<td>Trauma, n (%)</td>
<td>Assault 39 (55.7)</td>
<td>35 (50.0)</td>
<td>1.46, 0.94</td>
</tr>
<tr>
<td></td>
<td>Sexual assault 7 (10.0)</td>
<td>9 (12.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Accident 12 (17.1)</td>
<td>14 (20.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disaster 4 (5.7)</td>
<td>6 (8.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>War-related 4 (5.7)</td>
<td>3 (4.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other 4 (5.7)</td>
<td>3 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Clinical features</td>
<td>Earlier traumatic experiences, n (%)</td>
<td>40 (57.1)</td>
<td>0.60, 1, 0.44</td>
</tr>
<tr>
<td></td>
<td>Complex trauma 15 (21.4)</td>
<td>11 (15.7)</td>
<td>0.76, 1, 0.39</td>
</tr>
<tr>
<td></td>
<td>On psychoactive medication, n (%)</td>
<td>30 (42.9)</td>
<td>0.03, 1, 0.86</td>
</tr>
<tr>
<td></td>
<td>Antidepressants 13 (18.6)</td>
<td>12 (17.1)</td>
<td>0.05, 1, 0.83</td>
</tr>
<tr>
<td></td>
<td>Anxiolytics or opiates 18 (25.7)</td>
<td>23 (32.8)</td>
<td>0.86, 1, 0.35</td>
</tr>
<tr>
<td></td>
<td>Propranolol 3 (4.3)</td>
<td>2 (2.9)</td>
<td>1.00, 1</td>
</tr>
<tr>
<td></td>
<td>Antipsychotics 1 (1.4)</td>
<td>1 (1.4)</td>
<td>1.00, 1</td>
</tr>
<tr>
<td></td>
<td>Time since trauma in months (s.d.)</td>
<td>31.5 (50.6)</td>
<td>0.25, 138, 0.80</td>
</tr>
<tr>
<td></td>
<td>IES-R PTSD Total (s.d.)</td>
<td>79.9 (16.9)</td>
<td>2.25, 137, 0.03*</td>
</tr>
</tbody>
</table>

EMDR, eye movement desensitisation and reprocessing; IES-R, Impact of Event Scale-Revised; PTSD, post-traumatic stress disorder.

a. Low: completed elementary school or lower vocational education; Middle: completed high-school or middle level vocational education; High: completed pre-university, college, or university degree.

b. All met criterion A1 and A2 of DSM-IV.

c. Fisher’s exact test.

d. Significant at 0.05 level.
Reasons for treatment drop-out are given in Fig. 1. Participants who dropped out during sessions 4–8 scored higher on the IES-R than patients who continued treatment at those time points (all $P<0.001$). Non-completers were significantly younger than treatment completers ($t = -3.60$, d.f. = 138, $P<0.001$) and more likely to be of non-Dutch origin ($\chi^2 = 11.76$, d.f. = 1, $P<0.005$).

**Treatment integrity**

Of all the interventions started, 48 participants (37.8%, 24 for each condition) were randomly selected for independent scoring of protocol adherence by two raters. The overall mean treatment integrity score was 78 for brief eclectic psychotherapy (s.d. = 9.2) and 81 for EMDR (s.d. = 14.7). Thus, according to the raters, on average 78–81% of the desired elements of the treatment protocol were applied during the interventions. Kappa values ranged between 0.54 for brief eclectic psychotherapy and 0.75 for EMDR, which can be considered indicative of adequate to good agreement between the raters. Treatment integrity scores did not significantly differ for brief eclectic psychotherapy and EMDR ($t = 0.73$, d.f. = 37, $P = 0.48$).

**Main outcomes**

**Primary outcome**

The results of the intent-to-treat analyses of the primary outcome IES-R are shown in Fig. 2. The mixed-model analysis demonstrated a significant main effect of time ($F = 17.99$, d.f. = 1065, $P<0.001$), a significant main effect of treatment condition ($F = 12.20$, d.f. = 169, $P<0.005$) and a significant interaction between time and treatment condition ($F = 4.00$, d.f. = 1065, $P<0.001$). The response pattern proved to be significantly different for brief eclectic psychotherapy and EMDR ($t = 3.49$, d.f. = 169, $P<0.005$). The mean estimated difference on the IES-R between the treatment conditions across the 17 measurements was 13.10 (95% CI 5.69–20.50), corresponding with a large effect size (Cohen’s $d = 0.75$). Mean IES-R total scores at the second post-assessment for brief eclectic psychotherapy were 38.0 (s.d. = 34.4, $n = 41$) and for EMDR 28.5 (s.d. = 29.6, $n = 48$). At the second post-assessment, the difference between the treatment conditions was no longer significant ($t = 0.70$, d.f. = 340, $P = 0.48$; mean estimated difference 3.70 (95% CI –6.63 to 14.03)).
Additional analyses comparing IES-R scores after every two EMDR sessions with every three brief eclectic psychotherapy sessions showed that the response pattern was also significantly different for brief eclectic psychotherapy and EMDR ($t = 2.12$, d.f. = 139, $P<0.05$). Improvement effect sizes from baseline to second post-assessment were large for both treatment conditions (Cohen’s $d = 1.55$ for brief eclectic psychotherapy and Cohen’s $d = 1.73$ for EMDR). The completers-only analysis yielded comparable results for the IES-R scores.

**Secondary outcomes**

The mixed-model analysis of the SI-PTSD showed a significant main effect of time ($F = 37.06$, d.f. = 86, $P<0.001$), a significant main effect of treatment condition ($F = 11.05$, d.f. = 98, $P<0.005$) and a significant interaction between time and treatment condition ($F = 14.99$, d.f. = 86, $P<0.001$). The
response pattern proved to be significantly different for brief eclectic psychotherapy and EMDR ($t = 3.32$, d.f. = 98, $P<0.005$). Analysis by time point revealed that SI-PTSD scores were significantly lower for EMDR than for brief eclectic psychotherapy at the first post-assessment, but at the second post-assessment the difference was no longer significant (Table 2).

Improvement effect sizes from baseline to second post-assessment were large for both treatment conditions (Cohen’s $d = 1.95$ for brief eclectic psychotherapy and Cohen’s $d = 2.43$ for EMDR).

**Table 2.** Intent-to-treat analyses of the effects of treatment on clinician-rated post-traumatic stress disorder, depression and anxiety scores at baseline, first and second post-assessment

<table>
<thead>
<tr>
<th>Measure</th>
<th>Brief Eclectic Psychotherapy group</th>
<th>EMDR group</th>
<th>Effect sizes and mean estimated differences between the two groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean (s.d.)</td>
<td>N</td>
</tr>
<tr>
<td>SI-PTSD total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>70</td>
<td>40.11 (6.30)</td>
<td>70</td>
</tr>
<tr>
<td>First post-assessment</td>
<td>44</td>
<td>31.11 (12.47)</td>
<td>51</td>
</tr>
<tr>
<td>Second post-assessment</td>
<td>42</td>
<td>20.50 (12.79)</td>
<td>48</td>
</tr>
<tr>
<td>HADS depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>70</td>
<td>12.07 (4.05)</td>
<td>69</td>
</tr>
<tr>
<td>First post-assessment</td>
<td>41</td>
<td>8.68 (5.57)</td>
<td>51</td>
</tr>
<tr>
<td>Second post-assessment</td>
<td>42</td>
<td>7.38 (6.42)</td>
<td>48</td>
</tr>
<tr>
<td>HADS anxiety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>70</td>
<td>13.01 (3.94)</td>
<td>69</td>
</tr>
<tr>
<td>First post-assessment</td>
<td>41</td>
<td>10.17 (5.68)</td>
<td>51</td>
</tr>
<tr>
<td>Second post-assessment</td>
<td>42</td>
<td>8.02 (5.77)</td>
<td>48</td>
</tr>
</tbody>
</table>

EMDR, eye movement desensitisation and reprocessing; SI-PTSD, Structured Interview for Post-traumatic Stress Disorder; HADS, Hospital Anxiety and Depression Scale.

a. Raw values.
b. Cohen’s $d$, based on raw values.
c. Mean estimated differences from repeated-measures model with treatment condition, time, interaction time and treatment condition, and baseline value.

The mixed-model analysis on HADS depression scores revealed a significant main effect of treatment condition ($F = 8.72$, d.f. = 97, $P<0.005$) and a
significant interaction between time and treatment condition ($F = 5.61$, d.f. = 83, $P<0.05$), but no significant main effect of time ($P = 0.63$). The response pattern was significantly different for brief eclectic psychotherapy and EMDR ($t = 2.95$, d.f. = 97, $P<0.005$). Analysis by time point showed that HADS depression scores were significantly lower for EMDR than for brief eclectic psychotherapy at the first post-assessment, but at the second post-assessment the difference was not significant anymore (Table 2). Improvement effect sizes from baseline to second post-assessment were large for both treatment conditions (Cohen’s $d = 0.87$ for brief eclectic psychotherapy and Cohen’s $d = 1.21$ for EMDR).

Mixed-model analysis on HADS anxiety scores revealed a significant main effect of time ($F = 6.49$, d.f. = 83, $P<0.05$), a significant main effect of treatment condition ($F = 8.43$, d.f. = 98, $P<0.01$) and a significant interaction between time and treatment condition ($F = 14.90$, d.f. = 83, $P<0.001$). The response pattern was significantly different for brief eclectic psychotherapy and EMDR ($t = 2.90$, d.f. = 98, $P<0.01$). Analysis by time point showed that HADS anxiety scores were significantly lower for EMDR than for brief eclectic psychotherapy at the first post-assessment, but at the second post-assessment the difference was no longer significant (Table 2). Improvement effect sizes from baseline to second post-assessment were large for both treatment conditions (Cohen’s $d = 1.01$ for brief eclectic psychotherapy and Cohen’s $d = 1.38$ for EMDR).

We found similar results in the completers-only analyses of the SI-PTSD, HADS depression and HADS anxiety scores.

Numbers of patients with psychiatric diagnoses at the first and second post-assessment are shown in Table 3. Significant differences were found for PTSD and major depressive disorder at the first post-assessment; other differences were not significant.
Table 3. Psychiatric diagnoses at baseline, first and second post-assessment

<table>
<thead>
<tr>
<th></th>
<th>Brief Eclectic Psychotherapy group n/N (%)</th>
<th>EMDR group n/N (%)</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>( X^2 )</td>
</tr>
<tr>
<td>PTSD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>70/70 (100)</td>
<td>70/70 (100)</td>
<td></td>
</tr>
<tr>
<td>First post-assessment</td>
<td>21/44 (47.7)</td>
<td>4/51 (7.8)</td>
<td>19.38</td>
</tr>
<tr>
<td>Second post-assessment</td>
<td>6/42 (14.3)</td>
<td>3/48 (6.2)</td>
<td>0.30</td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>47/70 (67.1)</td>
<td>37/70 (52.9)</td>
<td>2.98</td>
</tr>
<tr>
<td>First post-assessment</td>
<td>16/44 (36.4)</td>
<td>7/51 (13.7)</td>
<td>6.60</td>
</tr>
<tr>
<td>Second post-assessment</td>
<td>8/42 (19.0)</td>
<td>7/48 (14.6)</td>
<td>0.32</td>
</tr>
<tr>
<td>Anxiety disorder other than PTSD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>14/70 (20.0)</td>
<td>8/70 (11.4)</td>
<td>1.94</td>
</tr>
<tr>
<td>First post-assessment</td>
<td>4/44 (9.1)</td>
<td>5/51 (9.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Second post-assessment</td>
<td>5/42 (11.9)</td>
<td>5/48 (10.4)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

EMDR, eye movement desensitisation and reprocessing; PTSD, post-traumatic stress disorder.

a. Structured Interview for Post-traumatic Stress Disorder.
b. Fisher’s exact test.
c. Structured Clinical Interview for DSM-IV Axis I Disorders.

Discussion

The current randomised controlled trial showed that EMDR and brief eclectic psychotherapy had equal effects in terms of reduction of self-reported and clinician-rated PTSD symptoms, depressive symptoms and general anxiety symptoms when statistically controlling for pre-treatment differences. Across all outcomes, the response pattern was significantly different for EMDR and brief eclectic psychotherapy when accounting for baseline differences, indicating that EMDR led to faster symptom decline and brief eclectic psychotherapy to more gradual improvement.
Efficacy and mechanism

Several explanations can be found for the faster symptom reduction in EMDR. First, the type of exposure to the traumatic event is different for brief eclectic psychotherapy and EMDR. In EMDR, short interrupted exposures to the ‘hotspots’ of the trauma are alternated with free association (which can involve moving quickly through scenes and associating with memories of other events that the person has experienced), and this associative process is seen as effective memory processing (Schubert & Lee, 2009). During brief eclectic psychotherapy, on the other hand, in every exposure session a part of the trauma is relived in great detail with a focus on experiencing grief, leading to more gradual trauma processing. The differences in exposure type and duration may explain the initial gradual change observed in brief eclectic psychotherapy and the faster change in EMDR. Due to the repetitive nature of interventions in both traditional prolonged exposure and EMDR, it is possible that the effects would be obtained faster than in brief eclectic psychotherapy. Further symptom reduction was observed for brief eclectic psychotherapy during the second treatment phase. So in this treatment the cognitive restructuring part, in which patients reflect on their trauma story and its meaning for their life, proved to be important for recovery from PTSD. Possibly, adding this phase to EMDR, as is sometimes done in clinical practice, could lead to further symptom reduction as well. Further research could address this by detailed study of the effective ‘ingredients’ of these treatments.

A second possible explanation for faster improvement with EMDR is that the session duration is 30–45 min longer than for brief eclectic psychotherapy. Additional analyses corrected for the difference in session duration still showed that EMDR led to faster symptom improvement. In this context it is interesting to note that strictly speaking the exposure time to the traumatic memory is shorter in EMDR than in brief eclectic psychotherapy. In brief eclectic psychotherapy the exposure is uninterrupted for 15–20 min, whereas in EMDR the exposure is limited to a few minutes in which the patient focuses on traumatic images. The session durations were those standard in clinical care and were therefore implemented as such in our study. Optimal session duration and frequency should be investigated in future research.
Chapter 4  

Comparison of our findings with previous studies

The results of our study are in line with previous trials that compared other trauma-focused CBT approaches with EMDR (i.e. the pilot study that found that EMDR leads to faster reduction in PTSD symptoms than trauma-focused CBT after a few sessions (Ironson et al., 2002) and trials reporting that both treatments led to equal improvements on PTSD symptoms post-treatment (Ironson et al., 2002; Vaughan, Armstrong, Gold, O’Connor, & Jenneke, 1994; Lee, Cavriel, Drummond, Richards, & Greenwald, 2002; Power et al., 2002; Taylor et al., 2003). Although the effects at the endpoint were equal, it should be noted that the current study cannot address with certainty whether the treatments are equivalent at that point because the confidence interval of the primary outcome contains the pre-specified difference of eight points (Jones, Jarvis, Lewis, & Ebbutt, 1996). This is attributable to the fact that the variance at the second post-assessment proved to be larger than we expected in our power analysis. The number of participants who completed their treatment and completed their assessment closely approximated the number of participants needed per arm in the power analysis, so we anticipate that drop out did not bias our results.

The magnitude of change in our trial is larger than in some previous studies. Although both baseline and post-treatment levels of the IES-R in our sample seem higher than in other studies, this is attributable to the different scoring method adopted by the Dutch version of the instrument. The PTSD improvement effect sizes from pre- to post-treatment for both brief eclectic psychotherapy and EMDR in our study were higher than those found across all active PTSD treatments in meta-analyses (Bradley et al., 2005; Bisson et al., 2007). The improvement effect sizes of EMDR in the current study were higher than the overall effect size for EMDR as reported in these meta-analyses, and brief eclectic psychotherapy improvement effect sizes were comparable with those of trauma-focused CBT.

Strengths and limitations

A strength of the current study is that we succeeded in comparing response patterns in two trauma-focused treatment protocols in a large, culturally diverse urban sample using a design that took into account sound methodology as well as clinical relevance. We emphasised scientific rigour by randomisation, protocol adherence, treatment integrity checks and independent assessment of outcome. The clinical meaningfulness of the results was increased by the inclusion of some elements of practical trials.
(trials that include elements of effectiveness designs), such as the inclusion of a heterogeneous trauma population, treatment duration dependent on the patients' recovery and the use of non-expert therapists.

We also recognise the limitations of our study. The foremost limitation is the drop out from both therapy and the assessments. However, the treatment drop-out rates of the current study are comparable with those in other trials (Hembree et al., 2003; Schnurr et al., 2007; Schottenbauer, Glass, Arnkoff, Tendick, & Gray, 2008). Interestingly, around 10% of patients dropped out before treatment, which might indicate a difficulty in starting trauma therapy. The drop-out rates from assessments were somewhat higher than in other studies, especially for brief eclectic psychotherapy. Nevertheless, for the primary outcome we were able to analyse a large proportion of the randomised patients because the data from the treatment sessions enabled us to calculate estimates of the response patterns if patients dropped out of later assessments.

A further limitation was that the number of brief eclectic psychotherapy exposure sessions fluctuated to a small degree, which could have exerted a small influence on our first post-assessment comparison. Finally, concurrent treatments such as pharmacological treatment, changes in pharmacological treatment and non-trauma-focused therapies may have contributed to the therapy effects for a minority of the patients. However, concurrent treatments were equally distributed across both brief eclectic psychotherapy and EMDR conditions and it may be presumed that they had an equal effect in both groups.

**Clinical implications**

In conclusion, this study demonstrates that both brief eclectic psychotherapy and EMDR are effective psychotherapeutic treatments, but EMDR may be a more time-efficient method for treating PTSD. Effect sizes and rates of diagnostic change were large for both treatment methods, indicating that the majority of people with PTSD benefit from trauma-focused psychotherapy. Symptom improvement appeared to occur at an earlier stage in EMDR than in brief eclectic psychotherapy, which may make patients more keen to choose this treatment method. However, brief eclectic psychotherapy may be preferred if patients value reflection on the trauma story and its meaning for their lives. Patient and therapist preferences have been shown to play an important role in the choice of treatment method (Van Minnen, Hendriks, & Olff, 2010). Because with both treatments patients dropped out, we should keep searching for new
therapeutic strategies (Schnyder, 2005). Future studies also need to prioritise investigating the reasons for premature treatment drop-out. Possibly, more attention should be given to psychoeducation and motivation to overcome persistent avoidance. This may especially be true for younger patients, those from minority ethnic groups and those who do not show symptom improvement over the first sessions and who drop out from treatment more frequently. Furthermore, future research needs to determine which patient groups benefit most from which form of psychotherapy. Finally, investigating long-term treatment effects is essential in order to offer individuals the best possible treatment option.

References


Chapter 4


Memory traces of trauma
Chapter 4


Chapter 5

Treatment of sexual trauma dissolves contamination fear: case report

Abstract

Background: In patients with co-morbid obsessive–compulsive disorder (OCD) and posttraumatic stress disorder (PTSD), repetitive behavior patterns, rituals, and compulsions may ward off anxiety and often function as a coping strategy to control reminders of traumatic events. Therefore, addressing the traumatic event may be crucial for successful treatment of these symptoms.

Objective: In this case report, we describe a patient with comorbid OCD and PTSD who underwent pharmacotherapy and psychotherapy.

Methods: Case Report. A 49-year-old Dutch man was treated for severe PTSD and moderately severe OCD resulting from anal rape in his youth by an unknown adult man.

Results: The patient was treated with paroxetine (60 mg), followed by nine psychotherapy sessions in which eye movement desensitization and reprocessing (EMDR) and exposure and response prevention (ERP) techniques were applied. During psychotherapy, remission of the PTSD symptoms preceded remission of the OCD symptoms.

Conclusions: This study supports the idea of a functional connection between PTSD and OCD. Successfully processing the trauma results in diminished anxiety associated with trauma reminders and subsequently decreases the need for obsessive–compulsive symptoms.
Introduction
The psychopathology of obsessive–compulsive disorder (OCD) and posttraumatic stress disorder (PTSD) shares the need for control as a core theme. OCD patients are obsessed with absolute certainty and try to control their anxiety provoking thoughts with repeated acts or rituals. PTSD patients try to regain control after experiencing an uncontrollable event by avoiding triggers of the event (Olff, Langeland, & Gersons, 2005). OCD and PTSD co-occur when a patient tries to control recollections of a traumatic event by means of obsessive–compulsive symptoms. It has been presumed that obsessive–compulsive symptoms may function as a coping strategy (Gershuny, Baer, Jenike, Minichiello, & Wilhelm, 2002), conveying the illusion of control in the midst of an uncontrollable event and its aftermath (Pitman, 1993).

Research into traumatized clinical samples has confirmed that OCD as well as PTSD may emerge after exposure to traumatic events, and that the content of the obsessive–compulsive symptoms may be associated with the trauma (De Silva & Marks, 1999; Gershuny, Baer, Wilson, Radomsky, & Jenike, 2003; Pitman, 1993; Sasson et al., 2005). Whereas the lifetime prevalence of PTSD is 7.4% (De Vries & Olff, 2009), the prevalence of PTSD in treatment-seeking OCD patients varies between 10.2% (Shavitt et al., 2009) and 39.4% (Gershuny et al., 2008), and the prevalence of OCD was found to be 40.9% in a sample of terror-and combat-related PTSD patients (Nacusch, Fostick, & Zohar, 2011). A case series in treatment-resistant OCD patients suggests that the co-occurrence of OCD and PTSD may hamper the effectiveness of treatment (Gershuny et al., 2003). In this case series, a treatment-induced decrease of OCD symptoms evoked an increase of PTSD symptoms, and vice versa an increase of OCD symptoms led to a decrease in PTSD-specific symptoms.

Objective
To this point, the sparse literature on concurrent OCD and PTSD has primarily been focused on determining comorbidity rates and on the impact of a trauma or PTSD on treatment response in OCD. In clinical practice, however, it is often very difficult to know what to treat first, OCD or PTSD? The aim of the current study is to examine whether treating PTSD by targeting the traumatic event facilitates OCD treatment. We describe an outpatient with OCD and PTSD who underwent trauma-focused
psychotherapy in addition to exposure and response prevention (ERP) treatment and pharmacotherapy.

Case report
Albert, a 49-year-old Dutch man who lives with his male partner, was referred to our department by his company doctor after 6 months of sickness absence from his work as a teacher. At intake, he met DSM-IV criteria for PTSD and OCD with daily trauma recollections, obsessions, and compulsions of cleaning and ordering for many hours a day. The trauma took place at the age of 14 when a 32-year-old man raped Albert. The PTSD symptoms started at the age of 21, when he first discussed what had happened with his partner. His OCD symptoms started at the age of 34, when he told a therapist about the trauma. Trauma recollections then evoked thoughts in his mind about feeling “dirty” (including his own body and surroundings). He tried to get rid of them by repeatedly showering, cleaning, exercising, and meticulously arranging things in his house.

After intake, paroxetine was started and increased to 60 mg, which improved his sleep and made him feel less anxious, though the diagnoses of PTSD and OCD remained. After 3 months, Albert received Eye Movement Desensitization and Reprocessing (EMDR) therapy in a randomized clinical trial (Nijdam, Gersons, Reitsma, de Jongh, & Olff, 2012). Written informed consent was obtained after the nature of the procedures was explained. The study design of the trial was approved by the Institutional Medical Ethics Committee and was performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). EMDR is a psychotherapeutic method in which the most distressing images of the traumatic event are identified and processed consecutively (De Jongh & Ten Broeke, 2004). Albert received nine psychotherapy sessions, of which seven consisted of EMDR. From session 6, when the PTSD symptoms markedly decreased, ERP techniques were added to tackle the remaining OCD symptoms.

Albert’s symptom course was closely monitored by means of widely used, reliable and valid instruments, as displayed in Table 1. Albert reported that the rationale for his obsessive–compulsive behavior ceased as soon as the trauma impact disappeared. The images of the traumatic event dissolved and he realized that he was not “dirty”, he felt less anxious, and was less compelled to perform his rituals. After 1 year, during which paroxetine treatment was continued, Albert is still free of PTSD and OCD
Chapter 5

Treatment of sexual trauma dissolves contamination fear: case report

Chapter 5

Treatment of sexual trauma dissolves contamination fear: case report

Table 1. Albert’s clinical diagnoses and symptom course before and after EMDR + ERP treatment

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline (t=0)</th>
<th>After EMDR + ERP (t=9 weeks)</th>
<th>Follow-up (t=17 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTSD diagnosis(^a)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>OCD diagnosis(^b)</td>
<td>Yes (severe OCD)</td>
<td>17 (moderate PTSD symptoms)</td>
<td>7 (subclinical PTSD symptoms)</td>
</tr>
<tr>
<td>PTSD symptom severity(^a)</td>
<td>33 (severe PTSD)</td>
<td>2 (subclinical PTSD symptoms)</td>
<td>0 (no PTSD symptoms)</td>
</tr>
<tr>
<td>OCD symptom severity(^c)</td>
<td>18 (moderately severe OCD)</td>
<td>Not available</td>
<td>1 (subclinical OCD symptoms)</td>
</tr>
<tr>
<td>Obsessions</td>
<td>9</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Compulsions</td>
<td>9</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Depressive symptom severity(^d)</td>
<td>4 (mild depressive symptoms)</td>
<td>0 (no symptoms)</td>
<td>0 (no symptoms)</td>
</tr>
<tr>
<td>Severity of general anxiety symptoms(^e)</td>
<td>7 (moderate general anxiety symptoms)</td>
<td>0 (no symptoms)</td>
<td>0 (no symptoms)</td>
</tr>
</tbody>
</table>

\(^a\) Structured Interview for PTSD, total possible score ranges from 0-68 (Davidson, Malik, & Travers, 1997); \(^b\) Structured Clinical Interview for DSM-IV disorders (Spitzer, Gibbon, Janet, & Janet, 1996); \(^c\) Impact of Event Scale – Revised, total possible score ranges from 0-110 (Weiss & Marmar, 1997); \(^d\) Yale-Brown Obsessive Compulsive Scale, total possible score ranges from 0-40 (Goodman et al., 1989); \(^e\) Hospital Anxiety and Depression Scale, total possible score ranges from 0-21 (Zigmond & Snaith, 1983).

Discussion

This case report demonstrates a successful treatment of comorbid OCD and PTSD, which hitherto has not been described in literature. We report on an outpatient with moderately severe OCD and severe PTSD, whose obsessive–compulsive symptoms commenced after revealing a sexual assault and were maintained by recollections of the trauma. The OCD and PTSD symptoms disappeared completely following a combined treatment with paroxetine and nine sessions of EMDR and ERP.

Our treatment strategy was based on the hypothesis that OCD symptoms serve as a strategy to cope with reminders of the trauma, which has been put forward by previous studies (Gershuny et al., 2002; Pitman, 1993). Unlike previous studies, PTSD symptoms in our study were targeted first with trauma-focused psychotherapy, followed by treatment of the OCD
symptoms with ERP techniques. Applying EMDR before ERP made it easier for the patient to reduce OCD symptoms because of decreased anxiety to trauma reminders. Our findings are in line with another case report that successfully applied trauma-focused cognitive behavioral therapy in combination with ERP techniques in PTSD with comorbid OCD symptoms (Tuerk, Grubaugh, Hamner, & Foa, 2009). The addition of EMDR, however, to ERP and SSRI has not yet been described previously. This case raises the question whether EMDR can be beneficial for OCD patients without a PTSD diagnosis. EMDR is increasingly applied for psychiatric disorders other than PTSD, if one or more causational events can be identified in their etiology. Mental images are reported by 81% of OCD patients, which often consist of memories of earlier adverse events (Speckens, Hackmann, Ehlers, & Cuthbert, 2007). The onset of OCD has been linked to an increased number of life events (McKeon, Roa, & Mann, 1984) and stressful events characterized by significant loss or increased responsibility (Rasmussen & Tsuang, 1986). With EMDR, mental images of those events could be targeted and their emotional distress can disappear.

Conclusions
To sum up, the current study supports the idea of a functional relationship between PTSD and OCD and suggests that trauma-focused psychotherapy may be useful in cases of concurrent PTSD and OCD originating from a traumatic event. By successfully processing the trauma, anxiety to trauma reminders decreases which may facilitate ERP treatment for OCD. This can lead to a shortened treatment trajectory and possibly an improved long-term treatment outcome. The findings are too preliminary to support widespread dissemination. Therefore, further research is encouraged to confirm these findings.

References
De Silva, P., & Marks, M. (1999). The role of traumatic experiences in the


---

*Memory traces of trauma*


Neurocognitive functioning over the course of trauma-focused psychotherapy: changes in verbal memory and executive functioning

Nijdam, M.J., Gersons, B.P.R., Reitsma, J.B., Martens, I.J.M., & Olff, M. Neurocognitive functioning over the course of trauma-focused psychotherapy: changes in verbal memory and executive functioning. Submitted.

Memory traces of trauma

85
Abstract

**Background.** Individuals with post-traumatic stress disorder (PTSD) have neurocognitive deficits in verbal memory and executive control. The origin of these deficits can be found in pre-trauma vulnerabilities, trauma exposure, or PTSD symptomatology, but remains unclear to date. In this study, we examined whether memory and executive functioning changed over the course of treatment and which clinical variables were associated with change.

**Methods.** Civilian trauma survivors (n = 88) diagnosed with PTSD received trauma-focused psychotherapy and completed a neuropsychological assessment at baseline and endpoint of a 17-week trial when treatments were finished. Neuropsychological tests administered were the California Verbal Learning Test, Rivermead Behavioural Memory Test, Stroop Color Word Test, and Trail Making Test. Assessments were performed in the context of a randomised controlled trial comparing Brief Eclectic Psychotherapy (n=41) and Eye Movement Desensitisation and Reprocessing therapy (n=47).

**Results.** Significant, small- to medium-sized improvements in verbal memory and executive functioning were found after trauma-focused psychotherapy (Cohen’s d 0.16 to 0.68). Greater PTSD symptom decrease was significantly related to better post-treatment neurocognitive performance (p<0.005). Patients with co-morbid depression improved more than patients with PTSD alone on interference tasks (p<0.01). No differences emerged between treatment conditions and between patients on serotonergic antidepressants and those who were not.

**Conclusions.** This study suggests that neurocognitive deficits in PTSD are at least partly reversible. This pattern of improvements is in line with studies showing normalised activity and morphological changes in prefrontal and limbic areas after trauma-focused psychotherapy, which is indicative of normalisation of the ‘fear network’.
Introduction

After exposure to a traumatic event, 1 in 9 people develop post-traumatic stress disorder (PTSD; Breslau et al., 1998; de Vries & Olff, 2009), a psychiatric disorder characterized by symptoms of re-experiencing, avoidance, and hyperarousal. Hyperarousal symptoms include enhanced attention for danger as well as diminished attention and forgetfulness for everyday activities. Neurocognitive studies in PTSD have also demonstrated the presence of attentional bias to threat-relevant information (Constans, 2005) and disturbances in attention and memory for emotionally neutral information, most consistently in verbal memory (Horner and Hamner, 2002; Brewin, Kleiner, Vasterling, & Field, 2007). Within the domain of emotionally neutral information, aspects of attention and memory dependent on executive control (e.g., inhibition, working memory, initial acquisition, sensitivity to distraction and interference) appear to be especially fragile in PTSD (Vasterling & Brailey, 2005). This neuropsychological profile is useful for survival in dangerous situations, because threat-related information is encoded in an efficient way and survival responses are rapidly initiated. It disrupts daily functioning, however, when it continues to exist in a non-threatening situation as is the case in PTSD.

Specific neural and neurobiological abnormalities found in PTSD, e.g. decreased activation of prefrontal areas, smaller hippocampal volumes and alterations in glucocorticoid levels, can be implicated as causes of impaired attention and memory (Qureshi et al., 2011). The hyperactivation of the amygdala seems most relevant to the information processing biases, whereas deficits on emotionally neutral tasks may be explained more directly by inhibition of the prefrontal cortex and smaller hippocampal volumes (Vasterling & Brailey, 2005).

So far, little is known about the origin of the neuropsychological abnormalities for emotionally neutral information. It is not yet clear whether they constitute a pre-trauma risk factor, whether they develop as a consequence of trauma exposure and/or the development of PTSD. Few longitudinal studies have been performed to address these questions. Two prospective studies on neuropsychological measures and its relationship to later PTSD symptoms found that worse neuropsychological performance before or shortly after the trauma predicted more PTSD symptoms post-trauma (Bustamante, Mellman, David, & Fins, 2001; Parslow & Jorm, 2007), giving some indications that it is a risk factor for developing PTSD. However,
Neurocognitive functioning over the course of trauma-focused psychotherapy: changes in verbal memory and executive functioning

the latter study also found some support that highly stressful experiences may have a detrimental effect on verbal memory, as also found by Vasterling et al. (2006) in a prospective study of a large deployed military cohort. Another eloquently designed study found evidence that neurocognitive differences in PTSD are most likely a familial pre-existing risk factor, demonstrating that veterans with PTSD did significantly differ from veterans without PTSD, but did not differ from their unexposed twins without PTSD on verbal memory, attention, and executive functioning (Gilbertson et al., 2006). A recent meta-analysis of cross-sectional studies showed that individuals with PTSD show more signs of cognitive impairment than trauma-exposed controls, and that cognitive impairment is positively correlated with severity of the PTSD symptoms (Qureshi et al., 2011). In sum, pre-trauma vulnerabilities, trauma exposure and the development of PTSD symptoms all seem to contribute to neurocognitive abnormalities in PTSD.

One of the ways to elucidate whether neuropsychological deficits are genuinely related to PTSD symptoms is to study alterations in PTSD patients before and after treatment. This tells us whether symptom improvement is associated with changes in neuropsychological functioning, and gives insight whether neuropsychological alterations are state-related instead of trait markers (Golier & Yehuda, 2002). Vermetten et al. (Vermetten, Vythilingam, Soutwick, Charney, & Brenner, 2003) showed that verbal memory performance significantly improved after treatment with paroxetine. Fani et al. (2009) attempted to replicate this study and found improvements after treatment, but failed to find a difference between the paroxetine group and the placebo control group. Furthermore, one small study has found improvements in some aspects of executive functioning after various forms of trauma-focused psychotherapy (Walter, Palmieri, & Gunstad, 2010). So far, no well-powered studies have investigated neuropsychological changes in response to trauma-focused psychotherapy.

The aim of the current study is therefore to examine longitudinal changes in neurocognitive functioning before and after trauma-focused psychotherapy, in the context of a randomised controlled trial. Furthermore, we investigated whether neuropsychological functioning changed differentially after two forms of trauma-focused psychotherapy, and whether symptom improvement was related to changes in neuropsychological performance. Additionally, we investigated if certain clinical variables were associated with neuropsychological change. Based on the previously mentioned studies indicating that SSRI treatment is
Neurocognitive functioning over the course of trauma-focused psychotherapy: changes in verbal memory and executive functioning

associated with neuropsychological improvement (Vermetten et al., 2003; Fani et al., 2009), we compared neurocognitive changes of patients who were on concurrent SSRI treatment to patients who received psychotherapy alone. Because we previously demonstrated that memory deficits are more severe in patients with PTSD and major depressive disorder (MDD; Nijdam & Olff, 2010), we also investigated whether patients who had a co-morbid MDD diagnosis showed different neuropsychological changes compared to patients with PTSD alone.

Methods

The current study was performed in the context of a randomised controlled trial comparing two forms of trauma-focused psychotherapy in PTSD patients: Brief Eclectic Psychotherapy and Eye Movement Desensitisation and Reprocessing therapy. Treatment completers in the EMDR condition received an average of 6.4 (S.D.=3.8) weekly sessions of 90 minutes whereas treatment completers in the BEP condition received an average of 14.7 (S.D.=4.5) weekly sessions of 45 minutes. A total of 140 patients were randomised to BEP (n=70) or EMDR (n=70), who all underwent neuropsychological assessment before starting their psychotherapy (t=0). A second neuropsychological assessment was completed by 88 patients after 17 weeks when both treatments were finished (t=17).

Participants

Participants were treatment-seeking outpatients who were referred to the Centre for Psychological Trauma at the Department of Psychiatry of the Academic Medical Centre in Amsterdam. Patients were included based on the following inclusion criteria: 1) fulfilling DSM-IV diagnostic criteria for PTSD; 2) having experienced a single traumatic event that was the immediate cause for developing PTSD and was ended at the time of inclusion; 3) age between 18 and 65 years; 4) mastery of the Dutch language in speech and writing. Exclusion criteria were: 1) acute suicidality; 2) the presence of current severe MDD or current severe alcohol or substance dependence according to DSM-IV; 3) the presence of a lifetime psychotic disorder according to DSM-IV; 4) fulfilling diagnostic criteria for a severe personality disorder according to the SCID-II screener and DSM-IV criteria for personality disorder. If patients were on pharmacological treatment, a stable regimen for at least one month was required before entering the study.
Chapter 6

Neurocognitive functioning over the course of trauma-focused psychotherapy: changes in verbal memory and executive functioning

Measures

Clinical measures

At pre-treatment and post-treatment assessment the following instruments were administered. A PTSD diagnosis was established by means of the Structured Interview for PTSD (Davidson et al., 1997), which operationalizes the DSM-IV criteria for PTSD. This interview consists of 17 items, each scored on a four-point scale. The items measure frequency and severity of PTSD symptom clusters and give an overall indication of PTSD severity. The SI-PTSD has good reliability and validity (Davidson, Malik, & Travers, 1997).

A Dutch translation of the Impact of Event Scale – Revised (IES-R) was used as a self-report of PTSD symptom severity (Weiss & Marmar, 1997). The IES-R questionnaire consists of 22 items, each measured on a four-point scale. Good psychometric qualities were found for the IES-R (Creamer, Bell, & Failla, 2003).

To assess co-morbidity, the Dutch version of the Structured Clinical Interview for DSM-IV Disorders (SCID-I) was administered (Spitzer, Gibbon, Janet, & Janet, 1996). The SCID-II screener (First, Gibbon, Spitzer, Williams, & Benjamin, 1997) was used to screen for personality disorders at baseline. High levels of reliability and validity were found for these instruments over time (Zanarini & Frankenburg, 2001).

Neuropsychological tests

Neuropsychological measures assessing verbal memory and executive functioning were administered to the participants pre- and post-treatment. Alternate versions of the memory tests were administered at the various time points to minimise practice effects.

The California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) is a multi-trial serial learning test thought to measure encoding, short-term retrieval, long-term retrieval and recognition of verbal information. A grocery list of 16 items is presented five times (List A), and patients are instructed to recall as many items as possible after each presentation. The sum of the correct responses on these first five trials is a measure of encoding performance (range of correct responses 0-80). Then a different list is presented and patients are asked to recall as many words as possible from this list (List B). Afterwards, patients are asked to recall List A at once (short-term retrieval; correct response range 0-16) and after an interval of 20 minutes (long-term retrieval; correct response range 0-16). Cued retrieval is measured by giving semantic cues to enhance recall, measured immediately (short-term cued retrieval) and after an interval of
Neurocognitive functioning over the course of trauma-focused psychotherapy: changes in verbal memory and executive functioning

20 minutes (long-term cued retrieval). Recognition memory is measured on a 44-item list including items of list A, B, and unfamiliar words; patients are asked to identify whether the word was part of List A or not (range of correct responses 0-44). Psychometric properties of the CVLT are sufficient (Paolo, Tröster, & Ryan, 1997).

The Paragraph Recall Subtest of the Rivermead Behavioural Memory Test (RBMT; Wilson, Cockburn, & Baddeley, 1985) is a test of short-term and long-term verbal memory. It is a test of everyday memory consisting of two newspaper excerpts read out loud to the patient. The patient is asked to recall the excerpt as exactly as possible directly after hearing it (short-term retrieval) and after an interval of 15 minutes (long-term retrieval). The sum of correctly recalled items on the two paragraphs, as defined by the manual, determines the test score (correct response range 0-42). The RBMT has shown to be a valid and reliable indicator of memory impairment in various populations (Wilson, Cockburn, Baddeley, & Hiorns, 1989).

The Stroop Color Word Test is thought to measure selective attention and cognitive flexibility (Homack & Riccio, 2003). This well-known test consists of three trials. With the first card patients are asked to read out loud colour names printed in black ink, in the second they are asked to name blocks of the same colours. On the third card the colour names are printed in incongruent ink (e.g. the word green printed in red ink), and patients are asked to name the colour of the ink. The interference score is calculated by the time in seconds used to complete the third card, minus the time in seconds on the second card. The reliability of the Stroop Color Word Test is sufficient (Strauss, Allen, Jorgensen, & Cramer, 2005).

The Trail Making Test (TMT) is a test to measure shift of attention, planning and cognitive flexibility (Reitan, 1955). Patients are asked to track a number sequence on a paper sheet (Part A) and a sequence of alternating numbers and letters (Part B) as fast as possible. The required time in seconds is measured and constitutes the score on the test. The time needed to complete part A and part B are both measures of mental speed, with part B focusing more on alternated attention. Reliability of the TMT is high for both parts (Lezak, 1995).

Procedure

Assessment and Follow-up

All subjects were outpatients who were assigned to the Centre for Anxiety Disorders at the Department of Psychiatry of the Academic Medical Centre

Memory traces of trauma | 91
of Amsterdam. At the start of the diagnostic assessment the procedure of the study was fully explained, after which patients were asked to participate and give their written informed consent. Patients were randomly assigned to either BEP or EMDR by computer, with a weighted maximum of subscribing four times the same treatment in a row. All assessments were carried out by psychologists or master’s level psychology students under supervision of an experienced psychologist, all blind to treatment condition. All therapists were fully trained and supervised in either BEP or EMDR protocols and instructed to stick to the protocol. Patient confidentiality was maintained. This study was approved by the Institutional Medical Ethics Committee of the Academic Medical Centre.

Treatments

EMDR
The weekly EMDR sessions lasted 90 minutes and were applied according to the Dutch treatment manual (De Jongh & Ten Broeke, 2004). During the EMDR procedure, the most distressing images of the traumatic event are identified and processed consecutively. After the patient has focused on an image with the corresponding negative cognition, the most distressing emotion and its bodily location, the patient is then continuously asked to follow the therapist’s finger making saccadic movements in alternation with the patient’s own associations. Current distress is rated every 5 to 10 minutes, until the distress level is 0 or 1, after which a more positive cognition is introduced in relation to the target image. This procedure is repeated for the other distressing images hierarchically and treatment sessions are ended when the trauma memory feels neutral. Auditory bilateral stimulation was used if problems with eye movements were encountered (e.g., if they induced headaches).

BEP
The BEP treatment is a manualized treatment consisting of weekly sessions of 45-60 minutes as administered in previous studies (Gersons, Carlier, Lamberts, & van der Kolk, 2000; Lindauer et al., 2005; Olff, De Vries, Güzelcan, Assies, & Gersons, 2007). Several of its techniques are similar to those used in cognitive behavioural therapy, such as psycho-education, imaginal exposure, writing assignments and cognitive restructuring. It also incorporates a focal psychodynamic approach, which is most prominent in the second phase of giving meaning to the traumatic event and in the farewell ritual, which is intended to symbolically leave the trauma behind.
Neurocognitive functioning over the course of trauma-focused psychotherapy: changes in verbal memory and executive functioning

The exposure in BEP differs from traditional CBT in focusing more on experiencing grief and in reliving the whole traumatic event – addressing the trauma part by part over several sessions.

Statistical Analyses
Analyses were conducted using SPSS version 18.0 (SPSS Inc., USA). Chi-square tests and independent t-tests were used to compare baseline demographic and clinical characteristics between the two treatment groups and between the total randomised group and the patients who completed the post-assessment. We used repeated-measures general linear models to address the main question if verbal memory and executive function change in PTSD patients after receiving trauma-focused psychotherapy. Within this model, we also tested whether verbal memory and executive function change differentially after BEP or EMDR treatment. The following analysis approach was used to examine changes on the different neuropsychological tests. The pre- and post-treatment scores were modelled as a function of time (two levels), treatment condition (two levels) and the interaction between time and treatment condition. Pearson correlation coefficients were used to determine whether PTSD symptom decrease was associated with change in neuropsychological performance and post-treatment performance. For the groups with and without co-morbid MDD and with and without SSRI use, several baseline differences emerged on the neuropsychological tests. Therefore, post- minus pre-treatment scores were calculated, and independent t-tests were used to determine whether these changes were equal for patients with PTSD and MDD compared to PTSD patients without MDD and whether patients who used SSRI’s in addition to their psychotherapeutic treatment showed different changes than patients who received trauma-focused psychotherapy alone. Two-tailed tests were applied throughout and significance was set at $\alpha=0.05$.

Results
Patients
A total of 140 patients took part in the randomized trial. Analyses were carried out on neuropsychological data from the 88 patients who took part in the neuropsychological assessment pre- and post-treatment. Of the 41 BEP patients, 35 had completed the treatment and 6 had dropped out of treatment prematurely. Of the 47 EMDR patients, 44 were treatment completers and 3 had dropped out prematurely. These treatment dropouts did complete the neuropsychological tests post-treatment. The 88 included
participants did not differ from the total randomised group of 140 patients regarding age, education, gender, ethnicity, co-morbid disorders, medication use and SSRI use, PTSD scores on SI-PTSD and IES-R, self-reported depression and anxiety scores on the HADS at the baseline assessment (all $p>0.05$), but the proportion treatment completers was greater in the included group ($p<0.001$).

Demographic and clinical characteristics for the patients in the treatment arms are displayed in Table 1. BEP and EMDR groups did not differ with respect to gender, education, ethnicity, co-morbid disorders, medication use and SSRI use, age, clinician-rated PTSD, and self-reported depression and anxiety (Table 1). A significant pre-treatment difference between the groups was found on the Impact of Event Scale – Revised; the BEP group had higher baseline self-reported PTSD scores than the EMDR group.

Regarding clinical response, BEP and EMDR were equally effective as illustrated by the comparable scores at the end of treatment on self-reported PTSD (mean difference 3.70; 95% CI=-6.63-14.03; $p=0.48$) and on clinician-rated PTSD (mean difference 2.41; 95% CI=-2.10-6.92; $p=0.29$), after controlling for scores at baseline (Nijdam, Gersons, Reitsma, De Jongh & Olff, 2012).
Chapter 6

Neurocognitive functioning over the course of trauma-focused psychotherapy: changes in verbal memory and executive functioning

Table 1. Demographic and clinical characteristics at baseline per treatment group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Brief Eclectic Psychotherapy (n=41)</th>
<th>Eye Movement Desensitisation and Reprocessing therapy (n=47)</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
<td>56.1</td>
<td>26</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>10</td>
<td>24.4</td>
<td>9</td>
</tr>
<tr>
<td>Middle</td>
<td>19</td>
<td>46.3</td>
<td>22</td>
</tr>
<tr>
<td>High</td>
<td>12</td>
<td>29.3</td>
<td>16</td>
</tr>
<tr>
<td>Dutch</td>
<td>26</td>
<td>63.4</td>
<td>31</td>
</tr>
<tr>
<td>Clinical features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-morbid axis I disorders (SCID-I, Patient Edition)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>25</td>
<td>61.0</td>
<td>22</td>
</tr>
<tr>
<td>Anxiety disorder other than PTSD</td>
<td>10</td>
<td>24.4</td>
<td>6</td>
</tr>
<tr>
<td>On psychoactive medication</td>
<td>17</td>
<td>41.5</td>
<td>18</td>
</tr>
<tr>
<td>On SRRI</td>
<td>9</td>
<td>22.0</td>
<td>8</td>
</tr>
<tr>
<td>Age</td>
<td>mean 39.0</td>
<td>S.D. 10.78</td>
<td>mean 41.6</td>
</tr>
<tr>
<td>PTSD Total score (SI-PTSD)</td>
<td>39.2</td>
<td>6.9</td>
<td>38.3</td>
</tr>
<tr>
<td>PTSD Total score (IES-R)</td>
<td>81.3</td>
<td>14.1</td>
<td>69.9</td>
</tr>
<tr>
<td>HADS Depression</td>
<td>11.7</td>
<td>3.9</td>
<td>11.0</td>
</tr>
<tr>
<td>HADS Anxiety</td>
<td>13.5</td>
<td>4.2</td>
<td>12.2</td>
</tr>
</tbody>
</table>

SCID-I, Structured Clinical Interview for DSM-IV Disorders; PTSD, Post-traumatic stress disorder; SSRI, Selective serotonin reuptake inhibitor; SI-PTSD, Structured Interview for Post-traumatic stress disorder; IES-R, Impact of Event Scale – Revised; HADS, Hospital Anxiety and Depression Scale.

Changes in neuropsychological performance

Means and standard deviations of the two groups on the neuropsychological measures at pre- and post-treatment are presented in Table 2. No significant differences were present at baseline on any of the measures between the two treatment conditions (all p>0.05). Repeated measurements analyses revealed a significant effect of time for all measures except CVLT long term cued recall. No significant interaction effects between time and treatment condition or main effects of treatment
Neurocognitive functioning over the course of trauma-focused psychotherapy: changes in verbal memory and executive functioning

condition were found (all \(p > 0.05\)). The magnitude of the improvements on the neuropsychological measures over time ranged from small- to medium sized (Cohen’s \(d\) 0.16 to 0.68).

### Table 2. Neuropsychological performance in the two treatment groups pre- and post-treatment

<table>
<thead>
<tr>
<th>Measure</th>
<th>Brief Eclectic Psychotherapy (n=41)*</th>
<th>Eye Movement Desensitisation and Reprocessing (n=47)*</th>
<th>Time effect</th>
<th>Time x treatment condition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-treatment</td>
<td>Post-treatment</td>
<td>Pre-treatment</td>
<td>Post-treatment</td>
</tr>
<tr>
<td></td>
<td>mean±S.D.</td>
<td>mean±S.D.</td>
<td>mean±S.D.</td>
<td>mean±S.D.</td>
</tr>
<tr>
<td>CVLT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sum</td>
<td>48.6±50.4</td>
<td>50.9±55.8</td>
<td>12.57</td>
<td>0.001</td>
</tr>
<tr>
<td>Trials 1-5</td>
<td>11.4 11.7</td>
<td>11.7 10.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST Free Recall</td>
<td>10.5±11.7</td>
<td>11.4±12.3</td>
<td>12.88</td>
<td>0.001</td>
</tr>
<tr>
<td>ST Cued Recall</td>
<td>11.9±12.0</td>
<td>12.2±13.2</td>
<td>6.63</td>
<td>0.01</td>
</tr>
<tr>
<td>LT Free Recall</td>
<td>11.2±12.0</td>
<td>11.7±13.0</td>
<td>13.00</td>
<td>0.001</td>
</tr>
<tr>
<td>LT Cued Recall</td>
<td>11.8±12.2</td>
<td>12.6±13.3</td>
<td>3.76</td>
<td>0.06</td>
</tr>
<tr>
<td>LT Recognition</td>
<td>4.0±2.8</td>
<td>4.1±4.2</td>
<td>8.03</td>
<td>0.006</td>
</tr>
<tr>
<td>LT</td>
<td>40.9±41.7</td>
<td>41.6±42.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBMT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate Recall</td>
<td>16.7±21.4</td>
<td>17.1±21.4</td>
<td>59.59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delayed Recall</td>
<td>12.7±17.3</td>
<td>13.8±17.6</td>
<td>46.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TMT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part A</td>
<td>35.7±32.0</td>
<td>34.4±27.9</td>
<td>20.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Part B</td>
<td>88.6±75.6</td>
<td>80.3±70.4</td>
<td>19.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroop</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Card 2</td>
<td>67.1±64.6</td>
<td>63.3±60.0</td>
<td>11.01</td>
<td>0.001</td>
</tr>
<tr>
<td>Card 3</td>
<td>111.7±102.6</td>
<td>104.4±94.8</td>
<td>8.24</td>
<td>0.005</td>
</tr>
<tr>
<td>Interference</td>
<td>44.8±38.3</td>
<td>42.1±35.2</td>
<td>5.44</td>
<td>0.02</td>
</tr>
<tr>
<td>Interference</td>
<td>32.1±37.9</td>
<td>37.1±34.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CVLT, California Verbal Learning Test; ST, Short Term; LT, Long Term; RBMT, Rivermead Behavioural Memory Test; TMT, Trail Making Test; \(d\), Cohen’s \(d\).

* Sample size varies slightly across observations because of missing data on a specific measure or outliers (total \(n=83-88\)).
Assessments of PTSD symptom decrease and neuropsychological performance

Because changes in PTSD symptoms and neuropsychological test scores were comparable between the two treatment groups, we combined the data from both groups for this analysis. Correlations between PTSD symptom decrease and neuropsychological test scores post-treatment are displayed in Table 3. Greater PTSD symptom decrease on the IES-R over the course of therapy was significantly related to better post-treatment scores on all neuropsychological measures, except Stroop interference. Correlations of similar strength and direction were found between decrease on each of the symptom clusters Reexperiencing, Avoidance, and Hyperarousal and all neuropsychological test scores post-treatment, except Stroop interference. We also investigated whether increase in neuropsychological performance was correlated with decrease in PTSD symptom severity over the course of treatment, but found no significant relationships (all \( p > 0.05 \)).

### Table 3. Pearson correlations between PTSD symptom decrease on the IES-R and post-treatment score on neuropsychological measures (n=88)\(^a\)

<table>
<thead>
<tr>
<th>Measure</th>
<th>IES-R Total decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CVLT</strong></td>
<td></td>
</tr>
<tr>
<td>Sum Trials 1-5</td>
<td>0.44*</td>
</tr>
<tr>
<td>ST Free Recall</td>
<td>0.36*</td>
</tr>
<tr>
<td>ST Cued Recall</td>
<td>0.40*</td>
</tr>
<tr>
<td>LT Free Recall</td>
<td>0.40*</td>
</tr>
<tr>
<td>LT Cued Recall</td>
<td>0.42*</td>
</tr>
<tr>
<td>LT Recognition</td>
<td>0.54*</td>
</tr>
<tr>
<td><strong>RBMT</strong></td>
<td></td>
</tr>
<tr>
<td>Immediate Recall</td>
<td>0.35*</td>
</tr>
<tr>
<td>Delayed Recall</td>
<td>0.32*</td>
</tr>
<tr>
<td><strong>TMT</strong></td>
<td></td>
</tr>
<tr>
<td>Part A</td>
<td>-0.46*</td>
</tr>
<tr>
<td>Part B</td>
<td>-0.43*</td>
</tr>
<tr>
<td><strong>Stroop</strong></td>
<td></td>
</tr>
<tr>
<td>Card 2</td>
<td>-0.39*</td>
</tr>
<tr>
<td>Card 3</td>
<td>-0.29*</td>
</tr>
<tr>
<td>Interference</td>
<td>-0.17</td>
</tr>
</tbody>
</table>

PTSD, Post-traumatic stress disorder; IES-R, Impact of Event Scale – Revised; CVLT, California Verbal Learning Test; ST, Short Term; LT, Long Term; RBMT, Rivermead Behavioural Memory Test; TMT, Trail Making Test.

\(^a\)Sample size varies slightly across observations because of missing data on a specific measure or outliers (total n=83-88).
Subgroup analyses

Subgroup analyses were performed to determine whether improvements were equal for patients with PTSD and MDD versus patients with PTSD alone, and for patients who received SSRI treatment during their psychotherapy versus patients who received psychotherapy alone. Because changes in PTSD symptoms and neuropsychological test scores were comparable between the two treatment groups, we combined the data from both groups for these analyses.

At baseline, PTSD patients with MDD (n=47) scored significantly worse than PTSD patients without MDD (n=41) on the following instruments: CVLT sum of trials 1-5 (mean difference 5.04; 95% CI=0.24-9.85; p<0.05), CVLT Short term cued recall (mean difference 1.40; 95% CI=0.30-2.50; p<0.05), RBMT delayed recall (mean difference 2.97; 95% CI=0.52-5.42; p<0.05), Stroop Card 2 (mean difference 8.17; 95% CI=0.73-15.62; p<0.05), Stroop Card 3 (mean difference 23.41; 95% CI=4.95-41.87; p<0.05), and Stroop interference (mean difference 15.50; 95% CI=1.66-29.33; p<0.05). When accounting for the baseline differences between the groups, patients with a co-morbid MDD showed similar improvement from pre- to post-treatment as individuals without MDD on most neurocognitive tasks, but improved more on Stroop Card 3 (mean difference 17.37; 95% CI=5.16-29.58, p=0.006) and Stroop interference (mean difference 14.98; 95% CI=4.11-25.85; p=0.007).

Baseline scores of patients with concurrent SSRI treatment (n=17) were significantly worse than patients who did not receive SSRI’s (n=71) on the following measures: CVLT sum of trials 1-5 (mean difference 8.86; 95% CI 2.94-14.79; p<0.005), CVLT Short term free recall (mean difference 1.97; 95% CI 0.35-3.58; p<0.05), CVLT Short term cued recall (mean difference 1.75; 95% CI 0.36-3.14; p<0.05), CVLT Long term free recall (mean difference 2.12; 95% CI 0.35-3.89; p<0.05), CVLT Long term cued recall (mean difference 2.29; 95% CI 0.77-3.81; p<0.005), CVLT Long term recognition (mean difference 1.96; 95% CI 0.20-3.71; p<0.05), TMT Part B (mean difference 30.37; 95% CI 11.72-49.02; p<0.005), Stroop Card 3 (mean difference 43.59; 95% CI 2.02-85.16; p<0.05) and Stroop Interference (mean difference 33.15; 95% CI 1.70-64.59; p<0.05). However, no significant differences were found in the improvement over time between these two groups (all p>0.05).
Discussion

Neurocognitive functioning after trauma-focused psychotherapy

To our knowledge, this is the first well-powered study to examine neurocognitive changes in response to trauma-focused psychotherapy. Results suggest that neuropsychological functioning improves over the course of trauma-focused psychotherapy, with significant, small- to medium-sized improvements in verbal learning and memory as well as executive functioning. Greater self-reported PTSD symptom improvement over the course of therapy was associated with better post-treatment scores on tests of verbal learning, memory, and executive functioning. Patients with co-morbid MDD showed similar improvement on most neurocognitive tasks as patients with PTSD alone, but improved more on interference tasks. No significant differences emerged between the EMDR and BEP treatment condition. There was no proof of any differences during psychotherapy between patients who were and who were not taking serotonergic antidepressants. These results extend the findings of a previous report of verbal memory improvement after pharmacological treatment (Vermetten et al., 2003). The results of the current study partly agree with a small study which found improvements in some aspects of executive functioning and not in others after a variety of psychotherapeutic treatments for PTSD (Walter et al., 2010). We found improvements on all our executive functioning measures for both treatment conditions. This difference is probably attributable to low statistical power in the Walter et al. study.

Our findings suggest that neuropsychological deficits in PTSD are at least partly related to PTSD symptoms. Deficits in verbal memory and executive functioning seem reversible after receiving EMDR or a trauma-focused cognitive behavioural intervention (BEP), which currently are the most effective treatments for PTSD. In addition, we demonstrated that PTSD symptom decrease over the course of treatment was related to post-treatment scores on neurocognitive measures. This study thus indicates that neuropsychological alterations in PTSD are state-related rather than only trait markers.

In line with our findings, some functional and morphological brain changes have been reported by other studies after PTSD treatment in areas which are involved in verbal memory and executive functioning. After EMDR and BEP, normalised activity in the dorsolateral prefrontal cortex has been reported by several studies (Levin, Lazrove, & van der Kolk, 1999; Lansing, Amen, Hanks, & Rudy, 2005; Oh & Choi, 2007; Lindauer et al.,
Neurocognitive functioning over the course of trauma-focused psychotherapy: changes in verbal memory and executive functioning

Results from those studies are somewhat more mixed regarding limbic areas, but lean towards decreased limbic activation. Moreover, EMDR responders showed increased hippocampal volumes (Bossini, Fagioliini, & Castrogiovanni, 2007), and increased posterior cingulate, anterior insula, and right para-hippocampal gyrus volumes (Nardo et al., 2009). Psychotherapeutic treatment thus seems to normalise the ‘fear network’ in PTSD by engaging executive functions in the prefrontal cortex and thereby subsequently inhibiting emotional responses in limbic structures (LeDoux, 2002). It can be presumed that these changes in turn lead to better executive functioning, learning, and memory.

Spontaneous recovery and practice effects are not likely causes of the improvements we found in this study. Had our patients not received treatment, natural recovery of PTSD and MDD symptoms could have presumably led to neurocognitive improvements. Though natural recovery occurs in acute PTSD in over half of the cases between 1 and 4 months, it is less likely in chronic PTSD, especially if individuals are also diagnosed with co-morbid MDD (Shalev et al., 1998). Since 89% of our participants had a diagnosis of chronic PTSD and 53% were diagnosed with MDD besides their PTSD, we do not believe spontaneous recovery of PTSD and MDD to be a likely explanation for our findings. Practice effects in the current study can be presumed to be minimal because of the use of alternate forms for the memory tests (Woods, Delis, Scott, Kramer, & Holdnack, 2006), the use of the TMT for executive functioning on which healthy participants in another study showed no practice effects (Basso, Bornstein, & Lang, 1999), and the time interval of 4 months between the assessments. Furthermore, Basso et al. argue that the magnitude of practice effects is smaller in clinical samples than in individuals without psychiatric disorders, since patients may not recall previous testing tasks to the same degree owing to their memory difficulties.

Strengths and limitations
The results of the current study should be considered in the context of several strengths and limitations. Strengths of the study are that we were able to include a relatively large sample of treatment-seeking PTSD patients, who had experienced different kinds of traumatic events and came from several cultural backgrounds. Moreover, because a randomised design was used we were able to assess the patients at fixed intervals, standardize the treatments they received and have them delivered with high treatment integrity. The design also allowed us to distinguish between

Memory traces of trauma

100
Neurocognitive functioning over the course of trauma-focused psychotherapy: changes in verbal memory and executive functioning

treatment conditions and investigate factors that possibly could have influenced neurocognitive improvements.

Several limitations should be noted as well. The results cannot address with certainty whether trauma-focused psychotherapy caused the improvement because for ethical reasons no control group was included in our study. Another limitation is that about one third of our original randomised sample did not complete the neuropsychological assessment at the end of treatment, and that our results are therefore more reflective of the improvements in treatment completers than of patients who dropped out of treatment prematurely. However, at baseline there were no other significant differences in clinical and demographic variables between patients who did and did not complete the second assessment. Finally, we did not assess other neurocognitive domains relevant to PTSD, such as different attention components and general intelligence, and we were not able to measure premorbid intelligence and neuropsychological performance pre-trauma.

Conclusion, implications and future directions

In sum, neurocognitive deficits present in PTSD can improve over the course of trauma-focused psychotherapy and are therefore at least partly reversible. The benefits in terms of PTSD symptom reduction during the course of treatment seem to translate into enhanced neurocognitive performance after treatment. Deficits found in PTSD are initially mild to moderate pre-treatment, but as Stein et al. (Stein, Kennedy, & Twamley, 2002) proposed, real-world situations involve more complex processing in comparison to the optimal test situation in which distraction is minimal. Improvements in verbal learning, memory and executive functioning in this study were small- to medium-sized, which seem modest in terms of magnitude. However, it can be argued that these differences translate to clinically relevant gains in the daily lives of patients, for instance in work performance, educational performance and interpersonal relationships. Future studies could further investigate these changes from pre- to post-treatment by linking neurocognitive outcomes with social and occupational functioning outcomes. Furthermore, future research could focus on stabilising neurocognitive performance pre-treatment by performing dual baseline assessments. These would plateau the practice effects and subsequent changes in performance would then primarily reflect the influence of interventions (McCaffrey & Westervelt, 1995). More longitudinal studies on different neurocognitive domains could also give insight into the separate contributions of pre-morbid vulnerabilities, trauma
exposure and PTSD symptoms. Preferably, this would take place in the context of groups at high risk for PTSD so that cognitive functioning can be assessed before and after trauma exposure, followed by subsequent treatment of individuals who develop PTSD to examine the reversibility of the alterations. More insight into the interplay between PTSD symptoms and neurocognitive alterations will ultimately enhance our understanding of the disorder and its treatment.

References


Neurocognitive functioning over the course of trauma-focused psychotherapy: changes in verbal memory and executive functioning


Chapter 6

Neurocognitive functioning over the course of trauma-focused psychotherapy: changes in verbal memory and executive functioning


Neuropsychological functioning over the course of trauma-focused psychotherapy: changes in verbal memory and executive functioning


Chapter 6

Neurocognitive functioning over the course of trauma-focused psychotherapy: changes in verbal memory and executive functioning


Chapter 7

Pretreatment low verbal memory is related to worse response to trauma-focused psychotherapy for posttraumatic stress disorder

Nijdam, M.J., de Vries, G.J., Gersons, B.P.R., & Olff, M. Pretreatment low verbal memory is related to worse response to trauma-focused psychotherapy for posttraumatic stress disorder. Submitted.
Chapter 7

Pretreatment low verbal memory is related to worse response to trauma-focused psychotherapy for posttraumatic stress disorder

Abstract

Background: Neuropsychological studies have consistently demonstrated impaired verbal memory in posttraumatic stress disorder (PTSD). Evidence-based trauma-focused treatment for PTSD is thought to rely on memory function, but it is largely unknown whether verbal memory performance is associated with treatment outcome. Our purpose was to examine the relationship between verbal memory performance and treatment response to trauma-focused psychotherapy.

Methods: Outpatients with PTSD were randomly assigned to Eye Movement Desensitization and Reprocessing therapy (EMDR; N=70) or Brief Eclectic Psychotherapy (BEP; N=70), a cognitive behavioral intervention. Neuropsychological measures administered pre-treatment were the California Verbal Learning Test (CVLT) and the Rivermead Behavioural Memory Test (RBMT). Response to trauma-focused psychotherapy was measured by self-reported decrease of PTSD symptom severity (Impact of Event Scale – Revised). Mixed linear model analyses were applied to determine the effect of treatment and the additional influence of the memory indices on treatment outcome.

Results: Lower baseline encoding, short-term retrieval, long-term retrieval and recognition performance were significantly associated with worse treatment response in terms of self-reported PTSD symptom severity for both treatment conditions. Using baseline long-term cued retrieval performance, 75.6% of the patients could be correctly classified as responder.

Conclusions: Attenuated verbal memory performance represents a risk factor for treatment response to trauma-focused psychotherapy. Verbal memory measures can be helpful in determining whether patients will benefit from trauma-focused psychotherapy. Future research should explore how treatment perspectives of patients with poor verbal memory can be improved.
Introduction

Symptoms such as re-experiencing a traumatic event in one’s mind, avoidance of thoughts about the trauma, and concentration problems characterize posttraumatic stress disorder (PTSD). PTSD may therefore be perceived as a disorder of memory (McNally, 2003), with terrifying events from the past being remembered far too well versus forgetfulness and decreased attention for everyday tasks which do not involve danger. Research has indeed confirmed the association between PTSD and several neuropsychological deficits in emotionally neutral material, which are most consistent in verbal memory and sustained attention (Horner & Hamner, 2002; Brewin, Kleiner, Vasterling, & Field, 2007; Johnsen & Asbjørnsen, 2008). Poor verbal memory performance has proven to be related to PTSD even when controlling for comorbidity (Gilbertson et al., 2006), attentional difficulties, and intelligence (Gilbertson, Gurvits, Lasko, Orr, & Pitman, 2001). Prospective studies have also shown that impairments in verbal memory, measured before or shortly after trauma, are a risk factor for developing PTSD symptoms later on (Bustamante, Mellman, David, & Fins, 2001; Parslow & Jorm, 2007).

According to various theories, there is an inverse association between verbal memory functioning and reexperiencing symptoms such as flashbacks and nightmares. Dual representation theory (Brewin, 2001; 2003; Brewin, Dalgleish, & Joseph, 1996) postulates that reexperiencing symptoms of PTSD are supported by a well-functioning image-based memory system (situationally accessible memory; SAM). The verbal memory system (verbally accessible memory; VAM), however, is presumed to function inadequately in patients with PTSD (Brewin, Dalgleish, & Joseph, 1996), with the result that the intrusions do no su bside. Several neurocognitive studies have provided evidence for a relationship between stronger reexperiencing symptoms and worse neuropsychological functioning. The more reexperiencing symptoms PTSD patients had, the worse their capacity to inhibit irrelevant information on emotionally neutral tasks (Vasterling, Brailey, Constans, & Sutker, 1998) and the worse their performance on verbal memory tasks (Parslow & Jorm, 2007; Johnsen, Kanagaratnam, & Asbjørnsen, 2008). The degree to which the memory system is deregulated thus seems to determine the extent to which patients can focus on everyday tasks that involve memory.

The most effective interventions for PTSD currently available are two trauma-focused psychotherapy methods: trauma-focused cognitive...
behavioral therapy (TF-CBT) and eye movement desensitization and reprocessing (EMDR) (Van Etten & Taylor, 1998; Bradley, Greene, Russ, Dutra, & Westen, 2005). Essential therapeutic elements of both approaches are a form of imaginal exposure and cognitive restructuring (Brewin, 2005). These therapeutic processes may be dependent on how well a person can store and retrieve new information. Therefore, verbal memory capacity may be predictive of successful outcome in therapy (Brewin & Holmes, 2003).

According to a meta-analysis, 44% of the patients who enter trauma-focused psychotherapy and 33% of the treatment completers continue to endorse criteria for PTSD (Bradley et al., 2005), but it is still largely unknown if the extent to which the memory system is deregulated hinders PTSD patients to benefit from treatment. So far, only a single study has provided evidence that verbal memory predicts treatment outcome in PTSD patients who underwent TF-CBT (Wild & Gur, 2008). Limitations of this study are its small sample size and its application of one type of psychological intervention. The aim of the current study is therefore to examine the relationship between verbal memory performance and treatment outcome in a larger sample and to different types of trauma-focused psychotherapy: EMDR and Brief Eclectic Psychotherapy (BEP), a form of TF-CBT. We hypothesized that poorer verbal memory performance for emotionally neutral information at baseline would predict worse treatment outcome in both conditions.

**Method**

**Participants and procedure**

Participants were treatment-seeking outpatients who were referred to the Center for Psychological Trauma at the Department of Psychiatry at the Academic Medical Center (AMC) of the University of Amsterdam. They were referred to the Center for Psychological Trauma by general practitioners, victim support workers, occupational physicians, and other AMC departments. If a PTSD diagnosis was presumed at intake, they were approached for participation in the study. A total of 140 patients were included and randomized to receive either EMDR (n=70) (De Jongh & Ten Broeke, 2004) or BEP (n=70) (Gersons, Carlier, Lamberts, & van der Kolk, 2000). Both treatments are highly structured manualized interventions. Treatment completers received an average of 6.5 (SD=3.8) EMDR sessions of 90 minutes or an average of 14.7 (SD=4.5) BEP sessions of 45 minutes.
Diagnostic assessments were performed by independent, trained assessors pre-intervention (T0), after the exposure phase (T1 = 6 weeks on average) and after both interventions were finished (T2 = 17 weeks). Neuropsychological measures were administered at T0. Patient confidentiality was maintained. The study protocol was approved by the Institutional Medical Ethics Committee of the AMC. After complete description of the study to the subjects, written informed consent was obtained.

Patients were included based on the following inclusion criteria: 1) PTSD according to DSM-IV; 2) a single traumatic event that was the immediate cause for developing PTSD and was finished at the time of inclusion; 3) age between 18 and 65 years; 4) mastery of the Dutch language in speech and writing. Exclusion criteria were: 1) acute suicidality; 2) current severe major depressive disorder (MDD) or current severe alcohol or substance dependence according to DSM-IV; 3) lifetime psychotic disorder according to DSM-IV; 4) severe personality disorder according to the SCID-II screener (First, Gibbon, Spitzer, Williams, & Benjamin, 1997) and DSM-IV criteria for personality disorder. Patients with a history of earlier trauma were allowed to participate. Patients with severe MDD or severe alcohol or substance dependence were allowed to participate after initial treatment for their conditions. If patients were on pharmacological treatment, a stable regimen for at least one month was required before entering the study.

Neuropsychological testing

Verbal memory was measured using the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) and the Rivermead Behavioural Memory Test (RBMT; Wilson, Cockburn, & Baddeley, 1985). The CVLT is a multi-trial learning test thought to measure encoding, short-term retrieval, long-term retrieval and recognition. A grocery list of 16 items is presented five times (List A), and patients are instructed to recall as many items as possible after each presentation. The sum of the correct responses on these first five trials is a measure of encoding performance (range of correct responses 0-80). After a distracting list (List B), patients are asked to recall List A at once (short-term retrieval; range 0-16) and after an interval of 20 minutes (long-term retrieval; range 0-16). Cued retrieval is measured by giving semantic cues to enhance recall, measured immediately (short-term cued retrieval; range 0-16) and after an interval of 20 minutes (long-term cued retrieval; range 0-16). Recognition memory is measured on a 44-item
list including items of list A, B, and unfamiliar words; patients are asked to identify whether the word was part of List A or not (range 0-44). Psychometric properties of the CVLT are sufficient according to a test-retest study (Paolo, Tröster, & Ryan, 1997).

The Paragraph Recall Subtest of the RBMT is a test of short-term and long-term retrieval. It is a test of everyday memory consisting of two newspaper excerpts read out loud to the patient. The patient is asked to recall the excerpt as exactly as possible directly after hearing it (short-term retrieval) and after an interval of 15 minutes (long-term retrieval). The sum of correctly recalled items on the two paragraphs, as defined by the manual, determines the test score (correct response range 0-42). The RBMT has shown to be a valid and reliable indicator of memory impairment in various populations (Wilson, Cockburn, Baddeley, & Hiorns, 1989).

**Treatment outcome measures**

Response to trauma-focused psychotherapy was determined based on the Impact of Event Scale – Revised (IES-R; Weiss & Marmar, 1997) and the Structured Interview for PTSD (SI-PTSD; Davidson, Malik, & Travers, 1997).

The IES-R is a 22-item self-report questionnaire which measures the severity of PTSD symptoms in the last 7 days. Unlike the original revised version in which categories from 0-4 are used, the Dutch IES-R rates the frequency of each item in the preceding week as 0 (not at all), 1 (rarely), 3 (sometimes), and 5 (often), resulting in a range of 0-110. The psychometric properties of the IES-R are sufficient (Creamer, Bell, & Failla, 2003).

The SI-PTSD is a structured interview which operationalizes the DSM-IV criteria for PTSD, consisting of 17 items each scored on a five-point scale (0-4, range of total score 0-68). An item score of 3 or higher was considered indicative of the presence of a specific symptom. The interview has good psychometric properties (Davidson et al., 1997; Carlier, Lamberts, Van Uchelen, & Gersons, 1998).

Demographic and clinical characteristics that could potentially influence neurocognitive performance were assessed at pre-treatment and controlled for in the analyses. A diagnosis of co-morbid depression was determined using the Structured Clinical Interview for DSM-IV Disorders (SCID-I; Spitzer, Gibbon, Janet, & Janet, 1996), a widely used interview with high reliability and validity (Zanarini & Frankenburg, 2001).
Data analysis

Chi-squared tests and independent t-tests were used to compare demographic and clinical characteristics between the treatment groups. Repeated measurement analyses were used to study changes over time between the treatment groups. Mixed linear model were used to take into account that measurements within the same individual are correlated, and to allow the model to calculate estimates when data were missing at certain assessments. An auto-regressive pattern was imposed on the covariance structure for measurements within the same individual (AR1). Outcome at the IES-R measure at the 17 post-measurements were modelled as a function of the intervention given (BEP, EMDR), time since intervention (categorical variable with 17 levels), baseline measurement of IES-R (continuous), baseline measurement of memory performance (Z-transformed, continuous), baseline assessment of having the diagnosis of major depressive disorder (yes, no), the interaction term between time and intervention, and the interaction term between memory performance and intervention. All analyses were carried out on an intent-to-treat basis unless indicated otherwise. To identify significant associations between variables Pearson correlation coefficients were calculated. P-values ≤ 0.05 were considered statistically significant and two-tailed tests were used throughout.

Results

Associations between individual memory measures

CVLT encoding had significant associations with all other CVLT indices (all r≥ .61, p<.001). CVLT short term free recall was significantly associated with other CVLT measures (all r≥.57, all p<.001). CVLT short term cued recall was found to be associated with all other CVLT indices (all r≥.56, all p<.001). CVLT long term free recall was significantly associated with all other CVLT measures (all r≥.64, all p<.001). CVLT long term cued recall was significantly associated with all other CVLT measures (all r≥.55, all p<.001). Finally, CVLT long term recognition was also significantly associated with all other CVLT measures (all r≥.55, all p<.001).

Both Rivermead immediate recall and delayed recall indices were found to be significantly associated with all CVLT indices (all r≥.29, all p≤.001). Rivermead immediate recall was significantly associated with Rivermead delayed recall (r=.86, p<.001).
Effect of individual memory measures on treatment outcome

Table 2 shows the results of the intent-to-treat analyses of the effects of memory and treatment on changes in post-traumatic stress disorder scores on the IES-R scale. The mixed-model analysis demonstrated a significant main effect of time (all \( p < .001 \)), a significant main effect of treatment condition (all \( p < .004 \)) and a significant interaction between time and treatment condition (all \( p < .001 \)). Even though the mixed-model analysis adjusted for the influence of memory performance on PTSD scores these effects were consistent with the results previously reported for this RCT (Nijdam, Gersons, Reitsma, de Jongh, & Olff, 2012). All individual memory measures influenced treatment outcome significantly (all \( p < .013 \)). Because the memory measures were all Z-transformed, the relative strength of effect of the individual measures could be reciprocally compared. CVLT long term cued retrieval demonstrated the largest strength of effect (\( \beta = -8.1; 95\% \text{CI} = [-12.7; -3.4]; t = -3.439; p = .001 \)). A negative strength of effect indicates that patients who perform better on the memory performance test will have a greater reduction in post-traumatic stress disorder scores on the IES-R scale. CVLT Measures of long term memory performance appeared to outperform short term memory performance (mean \( \beta = -7.4 \) vs. \( -5.3 \)). However the results on the Rivermead memory measures showed opposite effects (immediate retrieval: \( \beta = -5.6 \); delayed retrieval: \( \beta = -3.7 \)). No influence of memory performance on the effect of treatment condition was found (all \( p > .323 \)).

Baseline measurement of IES-R significantly affected PTSD scores at following time points (all \( p < .001 \)). Major depressive disorder at baseline was included in the analysis to control for the alternative interpretation that the influence of memory on PTSD scores is not due to the influence of depression on these values. The effect of depression on PTSD scores was found in half the models with CVLT short term free recall, CVLT long term memory recognition, Rivermead immediate and delayed memory retrieval (all \( p < .046 \)) as memory performance measures.
Chapter 7

Pretreatment low verbal memory is related to worse response to trauma-focused psychotherapy for posttraumatic stress disorder

Table 1. Intent-to-treat analyses of the effects of memory and treatment on changes in post-traumatic stress disorder (PTSD) scores on the Impact of Event Scale – Revised.

<table>
<thead>
<tr>
<th>Memory measure (Z-transformed)</th>
<th>Memory</th>
<th>Time</th>
<th>Condition</th>
<th>Time x Condition</th>
<th>Memory x Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>(SE)</td>
<td>F</td>
<td>P</td>
<td>F</td>
</tr>
<tr>
<td>CVLT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encoding</td>
<td>-5.2</td>
<td>(2.2)</td>
<td>17.565</td>
<td>&lt;.001</td>
<td>18.785</td>
</tr>
<tr>
<td>Retrieval, short term</td>
<td>-4.2</td>
<td>(2.3)</td>
<td>8.922</td>
<td>.003</td>
<td>18.402</td>
</tr>
<tr>
<td>Retrieval, long term</td>
<td>-6.8</td>
<td>(2.1)</td>
<td>23.703</td>
<td>&lt;.001</td>
<td>18.938</td>
</tr>
<tr>
<td>Cued retrieval, short term</td>
<td>-6.5</td>
<td>(2.3)</td>
<td>18.812</td>
<td>&lt;.001</td>
<td>18.856</td>
</tr>
<tr>
<td>Cued retrieval, long term</td>
<td>-8.1</td>
<td>(2.4)</td>
<td>21.808</td>
<td>&lt;.001</td>
<td>18.871</td>
</tr>
<tr>
<td>Recognition, long term</td>
<td>-7.2</td>
<td>(2.8)</td>
<td>13.238</td>
<td>&lt;.001</td>
<td>18.708</td>
</tr>
<tr>
<td>Rivermead</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrieval, short term</td>
<td>-5.6</td>
<td>(2.2)</td>
<td>15.688</td>
<td>&lt;.001</td>
<td>18.228</td>
</tr>
<tr>
<td>Retrieval, long term</td>
<td>-3.7</td>
<td>(2.3)</td>
<td>6.273</td>
<td>.013</td>
<td>18.068</td>
</tr>
</tbody>
</table>

CVLT, California Verbal Learning Test.

Simultaneous testing of the influence of memory measures on treatment outcome

Because all individual memory measures assessed at baseline were found to contribute to PTSD scores at following time points, we tried to determine which memory measures still contributed to the prediction of PTSD scores when all measures were compared simultaneously. Therefore, two separate mixed model analyses were performed in which we added all CVLT or all Rivermead measures to the model while removing the interaction between memory measure and treatment condition. The analysis with all CVLT measures incorporated in the model revealed that only CVLT short term free recall significantly influenced PTSD values (F(1, 145)=5.389, p=.022). When all Rivermead measures were incorporated into the model, the effect of the immediate memory recall was found to be statistically significant (F(1, 145)=12.195, p=.001). Thus, both CVLT and Rivermead...
analyses demonstrated the effects of short term memory performance on PTSD scores.

Can memory at baseline reliably predict treatment outcome?

The above findings raised the question whether memory performance at baseline could reliably predict treatment success in PTSD patients, with adequate sensitivity and specificity. To answer this question we fitted ROC curves for each memory measure with having remitted from the diagnosis of PTSD (defined as no longer fulfilling the criteria of the DSM-IV PTSD diagnosis) after 6 weeks of treatment (70 out of 95) and from the PTSD diagnosis at the end of treatment (81 out of 90) as reference. For remission from the PTSD diagnosis at 6 weeks after start of treatment, all memory measures showed reasonable areas under curve (AUCs) varying between .62 and .75. For remission of PTSD at the end of treatment, memory measures demonstrated AUCs ranging from .76 to .91. CVLT long term cued memory performance gave the highest AUCs for both time points (Figure 1). However, AUCs of most memory measures did not significantly differ from VLCT long term cued memory performance, except for CVLT long term memory recognition (Chi(1)=4.802, p=.028) and CVLT short term cued memory (Chi(1)=4.115, p=.043) only at 6 weeks after treatment. For instance, a cut-off point of 11 or higher of CVLT long term cued memory performance has a sensitivity of 74.1%, a specificity of 88.9% and a correct classification of 75.6% regarding the patients who were remitted from PTSD at the end of treatment.
Chapter 7

Pretreatment low verbal memory is related to worse response to trauma-focused psychotherapy for posttraumatic stress disorder

Discussion

This study investigated verbal memory performance for emotionally neutral information in PTSD patients before they underwent trauma-focused psychotherapy. The main finding is that lower verbal memory scores were robustly associated with worse treatment response. All the verbal learning and memory measures were significantly associated with the extent of decrease in self-reported PTSD symptoms. The effects of memory performance on PTSD scores were found to be strongest for delayed recall, were found both after the exposure phase of the treatments and at the endpoint of the treatments, and were found to be independent of treatment condition (BEP or EMDR). Good levels of sensitivity and specificity were found, with 75.6% of the patients being correctly classified as a responder to treatment (i.e., no longer fulfilling the criteria of the PTSD diagnosis). The effects for verbal memory performance were robust, since they were found to be independent of baseline severity of PTSD symptoms and major depression. These findings extend results of a small study that demonstrated the association between verbal memory and treatment response for TF-CBT in PTSD patients (Wild & Gur, 2008), and give support to the notion that verbal memory is related to treatment response in trauma-focused psychotherapy in general.

Figure 1. Receiver operating characteristic (ROC) curve for CVLT long term cued memory performance at 6 weeks and 17 weeks after treatment.
The present study suggests that the degree to which the memory system is dysfunctioning predicts whether PTSD patients can benefit from trauma-focused psychotherapy. According to dual representation theory, PTSD treatment generally targets both the image-based (SAM) and verbal memory system (VAM). Through a form of imaginal exposure to the traumatic event, information only present in the SAM is presumed to be reencoded into the VAM, leading to a subsequent reduction of re-experiencing symptoms (Brewin, 2005). Memories are assigned a spatial and temporal context in this process, and the person will be able to place the terrifying experiences and the sense of threat in the past. Our study shows that this therapeutic process is more restricted if PTSD patients have a more attenuated verbal memory performance at baseline. Fear responses, hypervigilance and other trauma-related emotions may not decrease sufficiently in this group of patients. A decrease of excessive fear reactions seems to be achieved in psychotherapy by strengthening ventromedial prefrontal cortex inhibition of the amygdala-mediated fear response (Quide, Witteveen, El-Hage, Veltman, & Olff, 2012). Interestingly, both smaller rostral anterior cingulate volumes and pre-treatment hyperresponsivity of the amygdala and ventral anterior cingulate during fear processing have been found to predict poor treatment response in TF-CBT (Bryant et al., 2008a,b). Different areas of the fear network thus seem to play a role in responding to trauma-focused psychotherapy, and the role of deficient prefrontal areas implicated in both verbal learning and fear extinction deserves further study.

Strengths of the current study are that we included a large sample of PTSD patients who met clinician-rated diagnostic criteria, that we used several verbal memory indices to investigate which aspects of verbal memory are most strongly related to treatment outcome independent of mediating factors, and that we randomly assigned patients to two forms of standardized trauma-focused psychotherapy. A limitation of this study was that we were not able to administer post-assessments to a substantial number of patients after their treatment, but we were able to calculate estimates for missing data points in the linear mixed model. A further limitation was that we could not control for intelligence because no such measure was administered. Overall intelligence is not likely to account for the findings of the current study, as it was not associated with treatment response in a previous study (Wild & Gur, 2008).

In summary, the current study demonstrates that the more attenuated verbal memory performance is in PTSD patients, the less likely
they are to benefit from trauma-focused psychotherapy. Memory measures may indicate who will benefit from treatment, and who will not. Advantages of verbal memory instruments are that they are non-invasive, easy to administer and limited in time required from professionals and PTSD patients, and therefore relatively easy to implement. Further research should emphasize improving treatment perspectives for patients scoring poorly on these tests. PTSD patients who perform poorly on verbal memory may need to be offered other interventions first, before receiving trauma-focused psychotherapy which is now the first choice treatment in several PTSD treatment guidelines. If it is presumed that these memory problems have been acquired by PTSD or coexisting disorders, it may be useful to offer this patient group SSRI’s first, as there is some evidence that these improve verbal memory (Vermetten, Vythilingam, Soutwick, Charney, & Brember, 2003). This may improve these patients’ ability to benefit from trauma-focused psychotherapy. Other possibilities are elementary adaptations to trauma-focused psychotherapy, such as adapting the pace and complexity of treatment, applying a more graduated approach to trauma recall and providing patients with reminders of the session content and homework, to reduce demands on verbal memory (Brewin, 2005).

Future research could further explore other potentially relevant factors for response to trauma-focused psychotherapy, such as sustained attention, which has also proven to be related to PTSD after controlling for mediators (Meewisse et al., 2007), and repeated exposure to threat stimuli (Brewin & Holmes, 2003). Visual memory is generally less impaired in PTSD than verbal memory (Brewin et al., 2007), therefore visual enhancers to the therapy could be beneficial. An attempt in this direction is virtual reality enhancement of imaginal exposure (Rothbaum, Rizzo, & Difede, 2010), which may facilitate retrieving and reliving the trauma memory. Although verbal memory deficits in PTSD may only be mild to moderate in terms of effect size (Horner & Hamner, 2002; Brewin et al., 2007), real-world situations involve more complex processing than a test situation in which distraction is minimal (Stein, Kennedy, & Twamley, 2002). This study demonstrates that even moderate verbal memory impairments may represent a risk factor for persistent PTSD in patients who are undergoing trauma-focused psychotherapy.

**References**


PTSD (SIP): Psychometric validation for DSM-IV criteria. *Depression and Anxiety, 5*, 127–129.


Hotspots in trauma memories and their relationship to successful trauma-focused psychotherapy: a pilot study

Abstract

Imaginal exposure is an essential element of trauma-focused psychotherapies for posttraumatic stress disorder (PTSD). Exposure should in particular focus on the “hotspots,” the parts of trauma memories that cause high levels of emotional distress which are often reexperienced. Our aim was to investigate whether differences in the focus on hotspots differentiate between successful and unsuccessful trauma-focused psychotherapies. As part of a randomized trial, 45 PTSD patients completed brief eclectic psychotherapy for PTSD. We retrospectively assessed audio recordings of therapy sessions of 20 patients. Frequency of hotspots and the associated emotions, cognitions, and characteristics were compared for the most successful ($n = 10$) versus the least successful ($n = 10$) treatments. The mean number of unique hotspots per patient was 3.20, and this number did not differ between successful and unsuccessful treatments. In successful treatments, however, hotspots were more frequently addressed ($r = .48$), and they were accompanied by more characteristics of hotspots ($r = .39$), such as an audible change in affect, indicating medium- to large-sized effects. Repeatedly focusing on hotspots and looking for associated characteristics of hotspots may help clinicians to enhance the efficacy of imaginal exposure for patients who would otherwise show insufficient response to treatment.
Chapter 8
Hotspots in trauma memories and their relationship to successful trauma-focused psychotherapy: a pilot study

Introduction

About 80% of people experience a traumatic event during their life, of whom 10% develop posttraumatic stress disorder (PTSD; De Vries & Olff, 2009). Trauma-focused cognitive-behavioral therapy (TF-CBT) and eye movement desensitization and reprocessing therapy (EMDR) are currently the most effective interventions for PTSD (Bradley, Greene, Russ, Dutra, & Westen, 2005). Brief eclectic psychotherapy (BEP; Gersons, Carlier, Lamberts, & van der Kolk, 2000) can be categorized as an integrative cognitive-behavioral intervention. Imaginal exposure to the trauma memory is applied in all these approaches to a certain degree, and is perceived as an essential element in their efficacy (Bradley et al., 2005).

Several models have been developed about why trauma memories continue to be relived by PTSD patients. According to Horowitz (1986), PTSD involves a biphasic alternation between reliving and avoiding the traumatic memory. After experiencing a trauma, the amount and nature of the information are too much to comprehend; therefore, the memory of the trauma is avoided or remembered in carefully controlled amounts. Because people have a fundamental need to integrate the new information of the traumatic experience, however, the traumatic memory is also actively brought into awareness by reexperiencing the sensory details of the event through flashbacks and nightmares. Contemporary cognitive theories have suggested that experiencing extreme stress, which depends on the individual's subjective appraisal of the threat (Ehlers & Clark, 2000; Olff, Langeland, & Gersons, 2005), is a crucial factor in altering the memory processing of the event (Brewin, Dalgleish, & Joseph, 1996). This could explain the intruding memories on one hand and the fragmented trauma memory, with lack of integration in space and time, on the other hand. Conway and Pleydell-Pearce (2000) suggest that especially intense feelings of surprise and unreality following an appraisal of overwhelming threat can lead to intrusions.

Dual representation theory (Brewin et al., 1996) postulates that reexperiencing symptoms are supported by a well-functioning image-based memory system (situationally accessible memory [SAM]), while the verbal memory system (verbally accessible memory [VAM]) tries to inhibit these symptoms but functions poorly in PTSD. If a person focuses on the intrusive memories when recovering from a trauma, information only present in the SAM becomes encoded in the VAM, by which new memories with a spatial and temporal context are created (Brewin, 2005). These two types of
memory will compete to determine which one is retrieved and when the new memory is salient enough, PTSD reactions will not reoccur. Ehlers et al. (2002) discovered that intrusive memories mainly represented stimuli that were present shortly before the moments of the trauma with the largest emotional impact. These warning signals could indicate impending danger if the person encountered them again, and are therefore logically connected to a sense of current threat. The content of the intrusions may guide the therapist towards the moments with the greatest emotional impact, also called “hotspots”, that have not been processed properly. Focusing on these hotspots in imaginal exposure is thought to bring about change in their meanings, which is assumed to be essential for reduction of PTSD symptoms (Ehlers, Hackmann, & Michael, 2004).

Case series showed that emotions such as anger, grief, shame, and guilt are often associated with hotspots (Grey, Holmes, & Brewin, 2001; Grey, Young, & Holmes, 2002), besides the typical PTSD criterion A2-emotions of anxiety, helplessness, and horror (American Psychiatric Association [APA], 2000). More systematic studies confirmed these findings, and found that approximately 80% of intrusions matched a hotspot, and identified a higher frequency of cognitive themes of psychological threat than physical threat in hotspots (Grey & Holmes, 2008; Holmes, Grey, & Young, 2005). Based on this broad spectrum of emotions and cognitions, a treatment strategy was proposed in which reliving was combined with cognitive restructuring (Ehlers & Clark, 2000; Grey, Young, & Holmes, 2002). According to Ehlers et al. (2004), imaginal exposure is not intended to ensure emotional habituation, but to identify hotspots and use these as a starting point for cognitive restructuring. In that way, new information can be added while reliving the trauma memory, which reduces the level of current threat.

The current study is the first to retrospectively assess the frequency and content of hotspots in BEP. Trauma-focused cognitive–behavioral interventions for PTSD imply that emotional engagement with the trauma memories leads to a reduction in severity of emotional distress. Hotspots are by definition the moments of the trauma that cause high levels of emotional distress. In line with previous research (Grey et al., 2002), we therefore explored the hypothesis that optimally addressing hotspots during exposure is essential for processing these moments and thereby for PTSD symptom reduction. Possibly, more hotspots would be identified in successful treatments than in unsuccessful treatments, or hotspots would be more frequently focused on during successful treatments in comparison to unsuccessful treatments. Along a similar vein, we expected that hotspots
in successful treatments would display more characteristics of hotspots as outlined in the manual of Holmes and Grey (2002), for example, the patient defines it as the worst moment, a change in affect, or a change from present to past tense when reliving the moment. These characteristics, more extensively described below, all indicate emotional engagement with the trauma memory and we therefore expected these more in successful treatments than in unsuccessful ones.

**Method**

**Participants and Procedure**

Participants were adult treatment-seeking PTSD patients at the Center for Psychological Trauma at the Academic Medical Center of the University of Amsterdam. Psychiatric diagnoses were confirmed by standardized clinical interviews. Patients were asked to participate in a randomized controlled trial and were randomized to receive either BEP \((N = 70)\) or EMDR \((N = 70)\). The study protocol was approved by the Medical Ethics Committee of the Academic Medical Center of the University of Amsterdam. All subjects signed written informed consent prior to participation. Further details of the study design are described elsewhere (Nijdam, Gersons, Reitsma, de Jongh, & Olff, 2012).

BEP is a manualized treatment that mainly consists of trauma-focused cognitive–behavioral elements such as psycho-education, imaginal exposure to the traumatic event, writing assignments, and cognitive restructuring (Gersons et al., 2000). Some elements can also be understood from other therapeutic approaches, i.e., objects that remind the person of the trauma, performing a farewell ritual, and meaning-making. Two phases can be distinguished in this treatment; from Sessions 2–6 imaginal exposure takes place, whereas Sessions 7–15 are dedicated to cognitive restructuring and giving meaning to the trauma. In the imaginal exposure, therapists address hotspots by letting the patient give a detailed account of their experiences at the moments with the greatest emotional impact before going further in the trauma narrative. Therapists also help the patient verbalize the emotions and cognitions connected to these moments.

BEP treatment completers \((n = 45)\) received an average of 14.7 \((SD = 4.5)\) sessions of 45–60 minutes in the trial. Data in the current article stem from the most successful \((n = 10)\) and least successful \((n = 10)\) BEP treatment completers, based on their decrease in PTSD symptom severity on the Dutch Impact of Event Scale-Revised (IES-R; Kleber & de Jong, 1998; Weiss & Marmar, 1997). Unlike the original revised version in which
categories from 0–4 are used, this Dutch IES-R rates the frequency of each item in the preceding week as 0 = not at all, 1 = rarely, 3 = sometimes, and 5 = often and the total PTSD score (range = 0–110) consists of the sum of all items. Demographic and clinical characteristics of the sample are displayed in Table 1. No significant differences were found in demographic and clinical characteristics between the two groups for gender ($p = .170$), ethnicity ($p = .474$), trauma type ($p = .424$), comorbid major depressive disorder ($p = .350$), and comorbid anxiety disorders ($p = .628$). The mean age of the total sample was 39.60 ($SD = 10.98$) and did not differ between the two groups ($U = 46.00, p = .762$).

| Table 1. Baseline demographic and clinical characteristics by group and total |
|-----------------------------------------------|----------------|----------------|----------------|
| Variable                        | Successfully treated ($n = 10$) | Unsuccessfully treated ($n = 10$) | Total ($n = 20$) |
| Gender (female)                | $n$ | % | $n$ | % | $n$ | % |
| Dutch                          | 8  | 80 | 4  | 40 | 12 | 60 |
| Ethnicity                      |     |    |     |    |     |    |
| Dutch                          | 8  | 80 | 7  | 70 | 15 | 75 |
| Indonesian                     | 0  | 0  | 2  | 20 | 2  | 10 |
| Surinamese                     | 1  | 10 | 0  | 0  | 1  | 5  |
| Aruban                         | 1  | 10 | 0  | 0  | 1  | 5  |
| Bosnian                        | 0  | 0  | 1  | 10 | 1  | 5  |
| Trauma type                    |     |    |     |    |     |    |
| Assault                        | 8  | 80 | 5  | 50 | 13 | 65 |
| Disaster                       | 1  | 10 | 1  | 10 | 2  | 10 |
| Sexual assault                 | 1  | 10 | 0  | 0  | 1  | 5  |
| Accident                       | 0  | 0  | 1  | 10 | 1  | 5  |
| War-related                    | 0  | 0  | 1  | 10 | 1  | 5  |
| Other                          | 0  | 0  | 2  | 20 | 2  | 10 |
| MDD                            | 5  | 50 | 8  | 80 | 13 | 65 |
| Anxiety disorder $^a$          | 4  | 40 | 2  | 20 | 6  | 30 |

Note. MDD = Major depressive disorder.
$^a$ Other than PTSD.

Audio recordings of all sessions in which imaginal exposure took place had to be complete to code all imaginal exposure sessions for frequency and content of hotspots. Participants received an average of 5.4 exposure sessions ($SD = 2.01$), leading to a total of 108 audio recordings to be coded. Of these, six were excluded because of poor quality of the recording. An independent assessor, blind with respect to treatment outcome and not involved in assessment or treatment, scored all audio recordings. A second
blind independent assessor scored 10% of the audio recordings to determine the reliability of the rating system.

Measure

The primary outcome was the number of hotspots based on the Hotspots Manual (Holmes & Grey, 2002). Secondary outcomes were characteristics of hotspots, cognitions, and emotions as defined in the manual. The coding task consisted of first, identifying the presence of a hotspot, and second, determining whether the nine characteristics of hotspots, the seven cognitive themes, and the 11 emotions were present or absent. The nine characteristics by which hotspots could be identified were (a) patient defines it as the worst moment, (b) moment has been identified as a hotspot in an earlier session, (c) audible change in affect, (d) changing from present to past tense when describing the event, (e) changing from the first person to the third person when describing the event, (f) “whizzed through” (describing the build up and aftermath of the event in great detail, but only cursory descriptions of the main event), (g) patient is unable to remember details of that moment, (h) patient is dissociating, and (i) intrusiveness (patient mentions that hotspot corresponds to an intrusion). The only adaptations of our manual in comparison to the original manual were that the “visible change in affect” was replaced by an “audible change in affect” because of the use of audio recordings, and that we removed the characteristic “high subjective units of distress (SUD)” because this rating scale is not applied in BEP. According to Holmes et al. (2005) and Grey and Holmes (2008), another recognizable element of a hotspot is intrusiveness, so this element was included in our adapted manual instead.

The seven cognition categories were (a) uncertain threat (unease, confusion, realization of a nonspecific threat, ongoing threat), (b) general threat of injury and death (self-dying, self will die, self injured, self will be injured, death or injury of others), (c) control and reasoning (interpersonal reasoning, planning, revenge/injustice), (d) consequences (consequences, relief, realization after), (e) abandonment (let down by others, outrage), esteem (self-blame/criticism), and (f) cognitive avoidance (disbelief, dissociation). The 11 emotion categories were fear, dissociation, sadness, surprise, anger, helplessness, shame, guilt, horror, disgust, and happiness. Only literally spoken words were coded. This means that a cognitive theme or emotion had to be mentioned literally by the therapist and/or patient in order to be coded as such according to the manual; no cognitive themes or emotions were inferred by the assessors. For coding of the A2 emotions as defined by the Diagnostic and Statistical Manual of Mental Disorders (4th
ed., text rev.; DSM-IV-TR; APA, 2000), the word “fear,” “helplessness,” or “horror” had to be used by the patient and/or therapist. The other eight emotions were coded as non-DSM-IV-TR A2 emotions.

Grey and Holmes (2008) found high interrater reliability for coding of emotions and cognitions (Cohen’s κ .84 and .82). To determine the interrater reliability of our adapted manual, two assessors first coded the exposure sessions of two participants (n = 11) for the presence of hotspots and then coded the presence or absence of characteristics of hotspots (n = 9), cognitive themes (n = 7), and emotions (n = 11) for every hotspot. Of the seven hotspots that were found, two were identified by only one assessor. The content of one of these two hotspots was identified as part of another hotspot by the other assessor, instead of coding it as a unique hotspot. The interrater reliability of our manual for characteristics of hotspots, cognitions, and emotions was found to be high, with Cohen’s κ of .86, .85, and .81, respectively.

Data Analysis

Statistical analyses were performed with IBM SPSS Statistics 19. Two-tailed independent Mann-Whitney tests and Fisher’s exact tests were used to compare successful and unsuccessful groups regarding demographic and clinical characteristics. Group differences on outcome variables were analyzed using one-tailed Mann-Whitney exact tests with Rosenthal’s r as effect size (Rosenthal, 1991). A p value of less than .05 was considered statistically significant.

Results

The baseline average IES-R score of the total sample was 83.55 (SD = 14.15) and did not differ between the two groups (U = 43.50, p = .623). Mean IES-R decrease of the total sample was 51.20 (SD = 27.56). For the successful and unsuccessful groups, average IES-R decrease was 75.50 (SD = 6.65) and 26.90 (SD = 15.72), with no overlap between the groups. The mean number of exposure sessions was 5.40 (SD = 2.01) and did not significantly differ between the two groups (U = 41.00, p = .485).

Hotspot findings are summarized in Table 2. Sixty-four hotspots were identified, and for all of the patients at least one hotspot was identified (range = 1–6). The mean number of unique hotspots per patient was 3.20 (SD = 1.61), and did not differ significantly between the successfully and unsuccessfully treated groups (U = 39.00, p = .218). During imaginal exposure, 31% of the hotspots were repeatedly focused on, meaning that these hotspots were addressed during imaginal exposure in
two or more sessions. Hotspots were more frequently addressed in successful treatments than in unsuccessful treatments ($U = 22.00, p = .018$), corresponding with a large-sized group difference (Rosenthal’s $r = .48$).

**Table 2. Differences in hotspots, emotions, and cognitions by group and total**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Successfully treated (n = 10)</th>
<th>Unsuccessfully treated (n = 10)</th>
<th>Total (n = 20)</th>
<th>$U$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unique hotspots</td>
<td>3.50 ± 1.58</td>
<td>2.90 ± 1.79</td>
<td>3.20 ± 1.61</td>
<td>39.0</td>
</tr>
<tr>
<td>Total hotspots$^a$</td>
<td>6.30 ± 3.20</td>
<td>3.20 ± 2.10</td>
<td>4.75 ± 3.10</td>
<td>22.0*</td>
</tr>
<tr>
<td>Characteristics of hotspots</td>
<td>4.70 ± 2.31</td>
<td>2.70 ± 2.98</td>
<td>3.70 ± 2.79</td>
<td>27.5*</td>
</tr>
<tr>
<td>Emotions</td>
<td>7.00 ± 2.71</td>
<td>5.70 ± 4.19</td>
<td>6.35 ± 3.50</td>
<td>37.0</td>
</tr>
<tr>
<td>Cognitions</td>
<td>5.40 ± 1.65</td>
<td>4.50 ± 3.17</td>
<td>4.95 ± 2.50</td>
<td>36.0</td>
</tr>
</tbody>
</table>

Note. $^a$Indexes the number of times that hotspots were addressed across all exposure sessions.

* $p < .05$, one-tailed.

Frequencies of identified characteristics of hotspots, emotions, and cognitive themes are shown in Table 2 and Table 3. The mean number of identified hotspots characteristics was significantly higher in the successfully treated group than in the unsuccessfully treated group ($U = 27.50, p = .045$), corresponding with a medium-sized group difference (Rosenthal's $r = .39$). No differences were found between the successfully versus unsuccessfully treated group in the mean number of emotions or cognitive themes (Table 2). No specific hotspots characteristics, emotions, or cognitive themes were more likely to be identified in hotspots of successfully versus unsuccessfully treated patients (largest $z = -1.45, -1.73$, and $-1.81$, respectively).
### Table 3. Mean frequencies and standard deviations for the separate hotspot characteristics, emotions, and cognitive themes in hotspots by group and total, sorted by decreasing size of the overall mean

<table>
<thead>
<tr>
<th>Variable</th>
<th>Successfully treated (n = 10)</th>
<th>Unsuccessfully treated (n = 10)</th>
<th>Total (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hotspot characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Audible change in affect</td>
<td>2.30 2.11</td>
<td>1.00 1.05</td>
<td>1.65 1.76</td>
</tr>
<tr>
<td>Previous hotspot</td>
<td>1.30 0.95</td>
<td>0.70 0.95</td>
<td>1.00 0.97</td>
</tr>
<tr>
<td>Whizzed through</td>
<td>0.40 0.70</td>
<td>0.50 0.71</td>
<td>0.45 0.69</td>
</tr>
<tr>
<td>Worst moment</td>
<td>0.50 0.71</td>
<td>0.30 0.48</td>
<td>0.40 0.60</td>
</tr>
<tr>
<td>Cannot remember details</td>
<td>0.10 0.32</td>
<td>0.20 0.42</td>
<td>0.15 0.37</td>
</tr>
<tr>
<td>Intrusive</td>
<td>0.20 0.42</td>
<td>0.00 0.00</td>
<td>0.10 0.31</td>
</tr>
<tr>
<td>Patient dissociates</td>
<td>0.10 0.32</td>
<td>0.00 0.00</td>
<td>0.05 0.22</td>
</tr>
<tr>
<td>From present to past tense</td>
<td>0.00 0.00</td>
<td>0.10 0.32</td>
<td>0.05 0.22</td>
</tr>
<tr>
<td>From first to third person</td>
<td>0.00 0.00</td>
<td>0.00 0.00</td>
<td>0.00 0.00</td>
</tr>
<tr>
<td>Emotions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fear</td>
<td>1.40 1.17</td>
<td>1.80 1.32</td>
<td>1.60 1.23</td>
</tr>
<tr>
<td>Helplessness</td>
<td>1.30 0.95</td>
<td>1.00 0.82</td>
<td>1.15 0.88</td>
</tr>
<tr>
<td>Anger</td>
<td>1.30 1.16</td>
<td>0.60 0.70</td>
<td>0.95 1.00</td>
</tr>
<tr>
<td>Sadness</td>
<td>1.00 0.82</td>
<td>0.60 1.07</td>
<td>0.80 0.95</td>
</tr>
<tr>
<td>Surprise</td>
<td>0.90 0.74</td>
<td>0.60 0.70</td>
<td>0.75 0.72</td>
</tr>
<tr>
<td>Disgust</td>
<td>0.40 0.70</td>
<td>0.20 0.63</td>
<td>0.30 0.66</td>
</tr>
<tr>
<td>Dissociation</td>
<td>0.40 0.70</td>
<td>0.20 0.63</td>
<td>0.30 0.66</td>
</tr>
<tr>
<td>Happiness</td>
<td>0.20 0.42</td>
<td>0.20 0.42</td>
<td>0.20 0.41</td>
</tr>
<tr>
<td>Shame</td>
<td>0.00 0.00</td>
<td>0.20 0.42</td>
<td>0.10 0.31</td>
</tr>
<tr>
<td>Guilt</td>
<td>0.00 0.00</td>
<td>0.10 0.32</td>
<td>0.05 0.22</td>
</tr>
<tr>
<td>Horror</td>
<td>0.00 0.00</td>
<td>0.00 0.00</td>
<td>0.00 0.00</td>
</tr>
<tr>
<td>Cognitions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General threat</td>
<td>1.60 1.17</td>
<td>0.80 0.63</td>
<td>1.20 1.01</td>
</tr>
<tr>
<td>Uncertain threat</td>
<td>0.80 0.63</td>
<td>1.30 1.34</td>
<td>1.05 1.05</td>
</tr>
<tr>
<td>Control and reasoning</td>
<td>0.70 0.67</td>
<td>0.90 0.74</td>
<td>0.80 0.70</td>
</tr>
<tr>
<td>Cognitive avoidance</td>
<td>0.80 0.79</td>
<td>0.50 0.71</td>
<td>0.65 0.75</td>
</tr>
<tr>
<td>Abandonment</td>
<td>0.70 0.95</td>
<td>0.40 0.70</td>
<td>0.55 0.83</td>
</tr>
<tr>
<td>Esteem</td>
<td>0.40 0.70</td>
<td>0.40 0.70</td>
<td>0.40 0.68</td>
</tr>
<tr>
<td>Consequences</td>
<td>0.20 0.42</td>
<td>0.00 0.00</td>
<td>0.10 0.31</td>
</tr>
</tbody>
</table>

In the total sample, PTSD criterion A2-emotions of fear, helplessness, and horror accounted for 34% of the identified emotions. Themes related to psychological threat (52%; abandonment, cognitive avoidance, consequences, control and reasoning, esteem) were slightly more often identified than themes associated with physical threat (48%; general threat, uncertain threat).
Chapter 8
Hotspots in trauma memories and their relationship to successful trauma-focused psychotherapy: a pilot study

Discussion
This pilot study retrospectively identified hotspots in trauma-focused psychotherapy and investigated their association with treatment outcome. The main finding was that hotspots were more often addressed during imaginal exposure in successful BEP treatments, as compared to unsuccessful treatments. In addition, hotspots in successful treatments were accompanied by more characteristics of hotspots, for instance, an audible change in affect. No significant difference was found in frequency of unique hotspots between successful and unsuccessful treatments, nor were hotspots in successful treatments characterized by a broader spectrum of emotions and cognitions than in unsuccessful treatments.

The current findings on frequency and content of hotspots largely correspond with the studies by Holmes’ group (2005, 2008). The number of identified hotspots in our study was somewhat lower than in those studies. This may be explained by the fact that an independent assessor retrospectively coded the hotspots in our study, instead of the therapist coding them subsequent to asking patients to describe their hotspots during exposure sessions. We replicated previous findings of a high percentage of emotions not present in the DSM-IV-TR PTSD A2 criterion, and a higher prevalence of cognitions associated with psychological than with physical threat.

Our main finding was that hotspots were more frequently addressed in successful treatments. This may be explained by dual representation theory (Brewin et al., 1996). This theory postulates that hotspots correspond to the moments where there was maximal functional separation between visuospatial and verbal processing, leading to a large discrepancy between the contents of the SAM and VAM memory systems (Brewin, 2005). Repeated exposure to the hotspots may be necessary for successful reencoding of all potential retrieval cues into the VAM to not trigger flashbacks. Interestingly, the number of unique hotspots did not significantly differ between successful and unsuccessful treatments. Probably, a certain number of peak emotional moments in the trauma story is characteristic of PTSD rather than of treatment success.

We note some limitations of our study. The current study is an explorative pilot study with small numbers, which may have had insufficient statistical power to detect all differences. Another limitation is that treatment dropouts were not included in the study. Findings on hotspots can possibly give directions regarding reasons why treatment was discontinued. Because a relatively large group of patients dropped out of
treatment prematurely, the difference in PTSD symptom improvement for successful versus unsuccessful groups was less widespread than expected. Further research with larger samples, treatment dropouts, and larger differences between groups is therefore much encouraged. This would also be necessary to investigate potential mediators, such as gender. Another limitation of the current study is the use of audio recordings instead of video recordings. This limitation probably mainly affected the identification of hotspot characteristics, such as a patient dissociating or blushing or sweating. We believe that identification of emotions and cognitions has not suffered from the use of audio recordings because the BEP therapists were explicitly instructed to help the patient verbalize emotions and cognitions when encountering a hotspot in imaginal exposure, and because the raters were instructed to code only literally mentioned emotions or cognitions. Finally, the reliability ratings of our manual suggested that it is sometimes hard to identify the boundaries of a hotspot.

The current findings suggest refinements for imaginal exposure during trauma-focused psychotherapy. Although we cannot draw causal inferences from this study, it seems important for successful therapy to repeatedly address the most difficult moments of the trauma memory, and to observe characteristics of hotspots during imaginal exposure. Repeated exposure to the trauma memory is applied in TF-CBT with the aim of achieving fear extinction (Foa & Rothbaum, 1998). Foa and Rothbaum suggest that trauma memories can be reactivated and changed by incorporating more accurate information. This idea is based on Lang's theory (1985), which suggests that knowledge about the traumatic experience can change by strengthening associations between a certain emotional network, and other incompatible networks. Effective behavioral strategies can therefore lead to cognitive changes and vice versa (Lovell, Marks, Noshirvani, Thrasher, & Livanou, 2001). Although fear extinction occurs secondarily in BEP, the main focus of the imaginal exposure is to address various other emotions, such as grief, helplessness, guilt, and shame. BEP assumes that fear of the intense emotions that the trauma has evoked hinders emotional processing of the trauma. One therapy goal is therefore to bring together the emotions and the trauma story. Expressing grief is considered very important in this process. Our current study points to the importance of observing hotspot characteristics during imaginal exposure, often consisting of an audible change in affect such as crying. An alternative approach for successful treatment of hotspots based on the work of Ehlers et al. (2004) is to apply cognitive restructuring techniques.
when addressing the hotspots during imaginal exposure, to change the meanings of the moments with the greatest emotional impact.

A possible implication of these findings is that recognizing and addressing non-fear-based hotspots may also enhance symptom reduction in other forms of trauma-focused cognitive–behavioral interventions. Therapists can pay close attention to the characteristics of hotspots as defined by Holmes and Grey (2002) when applying a form of imaginal exposure, and not only be focused on fear during exposure but also on emotions such as grief, helplessness, anger, surprise, and disgust. This might also translate to cognitive processing therapy in terms of identifying non-fear-based hotspots in written trauma narratives. In conclusion, findings on hotspots are highly relevant for clinicians, and can help them to enhance the efficacy of imaginal exposure for patients who would otherwise show insufficient response to treatment.

References


Chapter 8

Hotspots in trauma memories and their relationship to successful trauma-focused psychotherapy: a pilot study


Nijdam, M.J., Gersons, B.P.R., Reitsma, J.B., de Jongh, A., & Olff, M. (2012). Brief eclectic psychotherapy v. eye movement desensitisation and
Chapter 8

Hotspots in trauma memories and their relationship to successful trauma-focused psychotherapy: a pilot study


Dexamethasone-suppressed cortisol awakening response predicts treatment outcome in posttraumatic stress disorder

Abstract

Posttraumatic stress disorder (PTSD) has been associated with several alterations in the neuroendocrine system, most consistently with enhanced cortisol suppression in response to the dexamethasone suppression test. The aim of this study was to examine whether specific biomarkers of PTSD predict treatment success in trauma-focused psychotherapy. Data were collected in the context of a randomized controlled trial comparing two forms of trauma-focused psychotherapy. Basal cortisol and dehydroepiandosterone sulfate levels, and the response to the dexamethasone suppression test were assessed pre-treatment in 24 PTSD patients. Treatment success was measured by pre- to post-treatment decrease in self-reported PTSD severity. A more suppressed cortisol curve after dexamethasone significantly predicted greater PTSD symptom decrease in trauma-focused psychotherapy, independent of the effects of gender, major depressive disorder, and trauma history. Basal early morning cortisol and dehydroepiandosterone sulphate did not predict treatment response. This study suggests the use of the dexamethasone-suppressed test for the cortisol awakening response as a biomarker for treatment response to trauma-focused psychotherapy.
Introduction

Posttraumatic stress disorder (PTSD) is associated with several alterations in hypothalamic-pituitary-adrenal (HPA) axis functioning. Lower basal values of the stress hormone cortisol have been found in trauma survivors with PTSD under specific circumstances (Meewisse et al., 2007). Enhanced cortisol suppression has been found very consistently in PTSD populations in response to the dexamethasone suppression test (DST) (de Kloet et al., 2012), a procedure in which the HPA negative feedback loop is interrupted with a low dose of dexamethasone. Higher levels of dehydroepiandosterone (DHEA) and its sulphated metabolite (DHEAS) have also been demonstrated in PTSD patients (e.g., Kellner et al., 2010). In addition to its antiglucocorticoid effects, DHEA(S) is presumed to promote frontal lobe functioning and may contribute to extinction learning (Southwick et al., 2005).

Two forms of trauma-focused psychotherapy, trauma-focused cognitive behavioural therapy (TF-CBT) and eye movement desensitization and reprocessing therapy (EMDR), are currently the treatments of choice for PTSD. A few studies have investigated relationships between trauma-focused psychotherapy and HPA-axis functioning. These studies found an increase in basal cortisol and DHEA(S) levels after brief eclectic psychotherapy (BEP), a form of TF-CBT (Olff et al., 2007), whereas stress-induced cortisol levels in response to imaginal exposure to the trauma appeared to decrease in TF-CBT responders (Gerardi et al., 2010). Furthermore, a case report suggests that EMDR can also result in more attenuated cortisol hypersuppression in response to the DST (Heber et al., 2002). One study found lower pre-treatment activity of the cortisol metabolite 5α-reductase among TF-CBT non-responders as compared to responders (Yehuda et al., 2009).

So far, neuroendocrine predictors of treatment response have hardly been studied in PTSD, and dexamethasone-suppressed cortisol and DHEAS have not yet been investigated in association with trauma treatment outcome. Testing the responsivity of the neuroendocrine system by using challenge tests may provide more insight into the dynamics of the system, which can possibly help predict treatment response (Olff et al., 2007). Therefore, our aim was to investigate whether specific PTSD biomarkers predict treatment response in trauma-focused psychotherapy. Pre-treatment cortisol and DHEA(S) were investigated, both under basal conditions and in response to DST, and related to the PTSD symptom
Dexamethasone-suppressed cortisol awakening response predicts treatment outcome in posttraumatic stress disorder
decrease over treatment. We hypothesized that dexamethasone-suppressed cortisol would be a marker of response due to its predicting role in previous studies of treatment for MDD and comorbid PTSD (e.g., Watts and Groft, 2010). DHEAS was expected to predict response because of its presumed role in extinction learning.

Methods

Participants and procedure
Participants were adult treatment-seeking PTSD patients at the Center for Psychological Trauma at the Academic Medical Center (AMC) at the University of Amsterdam. Psychiatric diagnoses were confirmed by structured clinical interviews. They participated in a larger randomised controlled trial comparing two forms of trauma-focused psychotherapy in 140 PTSD patients: EMDR and BEP. Treatment completers in the EMDR condition received an average of 6.5 (S.D.=3.8) weekly sessions of 90 min whereas treatment completers in the BEP condition received an average of 14.7 (S.D.=4.5) weekly sessions of 45 min in agreement with treatment protocols. Clinical post-treatment assessments were completed at 17 weeks after start of treatment. Written informed consent was obtained after full explanation of the study procedures. Further details of the study procedure have been described elsewhere (Nijdam et al., 2012).

Collection of neuroendocrine measures was optional and a subgroup of 26 patients completed these before starting treatment. Two patients dropped out before treatment and were excluded. The remaining 24 patients comprise the sample of this study; 13 of them were randomly assigned to BEP and 11 to EMDR. Prior to entering the trial, patients who were on parallel pharmacological treatment were required to be on a stable medication dose for at least 4 weeks, and patients with prior alcohol or substance dependence were required to be abstinent for at least 3 months. No patients used oral contraception.

Clinical measure
Primary outcome for measuring treatment response was the pre- to post-treatment change on the Impact of Event Scale – Revised (IES-R; Weiss and Marmar, 1997). Unlike the original revised version in which categories from 0-4 are used, this Dutch IES-R rates the frequency of each item in the preceding week as 0 (not at all), 1 (rarely), 3 (sometimes), and 5 (often), resulting in a range of 0-110. The instrument has good psychometric properties (Creamer et al., 2003).
Routine somatic screening was performed on all participants. Participants sampled saliva during two consecutive similar days at home with strict reference to awakening time (after 0, 15, 30, and 45 min, as well as after 4 and 14h). Salivary cortisol and DHEAS were assessed under basal conditions on the first day; at 2300h that day patients ingested 0.5 mg dexamethasone to assess the sensitivity of the HPA-axis on the second day. On the second day, samples were taken at the first four time points. Patients filled out the exact sampling times to ensure adherence to the correct time intervals. Saliva was collected using Salivettes (Sarstedt, Etten-Leur, The Netherlands). Patients were asked to refrain from eating, toothbrushing, and drinks other than water until after the fourth morning sample, and 1h before the fifth and sixth sample on day one. They were asked to refrain from alcohol on both days, and from smoking 2h before sampling. Participants kept the samples refrigerated before they were stored at -20°C until assay. Samples were analysed by immunoassay (DPC, Breda, The Netherlands).

**Trauma-focused psychotherapy**

In EMDR the most distressing images of the traumatic event are identified and processed. After the patient has focused on an image with the corresponding negative cognition, the distressing emotion and its bodily location, the patient is continuously asked to follow the therapist’s finger making saccadic movements in alternation with the patient’s associations. Distress is rated every 5 to 10 min, until the distress level is 0 or 1, after which a more positive cognition is introduced in relation to the target image. Treatment sessions are ended when the trauma memory feels neutral.

The main treatment components of BEP are similar to other trauma-focused cognitive behavioral therapy protocols, such as psychoeducation, imaginal exposure, writing assignments and cognitive restructuring. Two main phases can be clearly distinguished; from session 2-6 imaginal exposure takes place, and session 7-15 is dedicated to cognitive restructuring. Session 1 consists of psycho education and session 16 of a farewell ritual. Some elements of the second phase can also be understood from other therapeutic perspectives, e.g., taking objects to the therapy that are linked to the trauma, giving meaning to the trauma and the farewell ritual.
Chapter 9

Dexamethasone-suppressed cortisol awakening response predicts treatment outcome in posttraumatic stress disorder

**Statistical analysis**

Statistical analyses were performed with IBM SPSS Statistics 19. Areas under the curve with respect to ground (AUC) were calculated to integrate data from the first four measurements. To examine the association between neuroendocrine data and treatment response, linear regression analyses were performed with the AUC of the hormone, gender, major depressive disorder (MDD), and previous chronic trauma in youth as independent variables and pre- to post-treatment change in IES-R as dependent variable. If the post-treatment assessment was not completed, the IES-R score from the last session was carried forward as post-treatment value. The controlling variables were selected because of their association with neuroendocrine data in previous studies (Meewisse et al., 2007; Olff et al., 2007). Afternoon and evening hormone levels did not significantly predict outcome and were therefore not presented. Because of equal treatment effects after 17 weeks (Nijdam et al., 2012), the two intervention groups were analyzed together.

**Results**

**Patients**

Baseline demographic, clinical, and neuroendocrine characteristics of the sample are displayed in Table 1. Of the 24 patients, 19 were treatment completers and 5 had dropped out of treatment prematurely. Mean IES-R change from pre- to post-treatment was 41.71 (SD=34.5); a significant decrease, t(23)=5.92, p<.001. At post-treatment, 20 out of 21 patients no longer fulfilled criteria for PTSD and 11 out of 15 lost their diagnosis of MDD.
Dexamethasone-suppressed cortisol awakening response predicts treatment outcome in posttraumatic stress disorder

Table 1. Baseline demographic, clinical and neuroendocrine characteristics of the sample (n=24)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>11</td>
<td>46</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>7</td>
<td>29</td>
</tr>
<tr>
<td>Middle</td>
<td>10</td>
<td>41</td>
</tr>
<tr>
<td>High</td>
<td>7</td>
<td>29</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/living together</td>
<td>11</td>
<td>50</td>
</tr>
<tr>
<td>Single</td>
<td>12</td>
<td>46</td>
</tr>
<tr>
<td>Divorced</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutch</td>
<td>15</td>
<td>62</td>
</tr>
<tr>
<td>Surinamese</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>Turkish</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Moroccan</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assault</td>
<td>12</td>
<td>50</td>
</tr>
<tr>
<td>Accident</td>
<td>8</td>
<td>33</td>
</tr>
<tr>
<td>Sexual assault</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>War-related</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Smoking</td>
<td>8</td>
<td>33</td>
</tr>
<tr>
<td>Co-morbid axis I disorders (SCID-I)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>15</td>
<td>63</td>
</tr>
<tr>
<td>Anxiety disorder other than PTSD</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>On psychoactive medication</td>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Previous traumatic experiences</td>
<td>12</td>
<td>50</td>
</tr>
<tr>
<td>Chronic youth trauma</td>
<td>5</td>
<td>21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>PTSD Total score on SI-PTSD</td>
</tr>
<tr>
<td>PTSD Total score on IES-R</td>
</tr>
<tr>
<td>Basal Cortisol AUC</td>
</tr>
<tr>
<td>Post-DST Cortisol AUC</td>
</tr>
<tr>
<td>Basal afternoon cortisol</td>
</tr>
<tr>
<td>Basal evening cortisol</td>
</tr>
<tr>
<td>Basal DHEAS AUC</td>
</tr>
<tr>
<td>Post-DST DHEAS AUC</td>
</tr>
<tr>
<td>Basal afternoon DHEAS</td>
</tr>
<tr>
<td>Basal evening DHEAS</td>
</tr>
</tbody>
</table>

Note. SCID-I, Structured Clinical Interview for DSM-IV axis I disorders; PTSD, posttraumatic stress disorder; SI-PTSD, Structured Interview for Posttraumatic Stress Disorder; IES-R, Impact of Event Scale-Revised; AUC, Area under the curve with respect to ground; DST, Dexamethasone suppression test; DHEAS, Dehydroepiandosterone sulfate.

Memory traces of trauma | 147
Chapter 9

Dexamethasone-suppressed cortisol awakening response predicts treatment outcome in posttraumatic stress disorder

**Neuroendocrine predictors of response to treatment**

Results of the regression analyses are displayed in Table 2. Of the hormones studied, only the cortisol awakening curve after DST significantly predicted IES-R decrease together with the controlling variables gender, baseline MDD and previous chronic youth trauma, $F(4,17)=4.99$, $p=0.008$, $R^2=0.54$. Chronic youth trauma contributed at trend level, $t=1.88$, $p=0.077$. Greater PTSD symptom decrease was thus significantly associated with having a more flattened cortisol awakening curve after administration of dexamethasone, and at trend level with no previous chronic youth trauma.

In two of the other regression analyses, gender significantly contributed to the prediction of PTSD symptom severity change (all $p<0.031$). Female participants had greater PTSD symptom decline. The presence of previous chronic youth trauma contributed to two of the other regression analyses (all $p<0.048$). Greater PTSD symptom decrease was associated with no chronic youth trauma.

Table 2. The predictive effect of each individual stress hormone on change in PTSD severity as measured by the Impact of Event Scale – Revised from pre- to post-treatment ($n=22$)

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Change in PTSD severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coef.</td>
</tr>
<tr>
<td>Basal Cortisol AUC</td>
<td>-0.001</td>
</tr>
<tr>
<td>Post-DST Cortisol AUC</td>
<td>-0.034</td>
</tr>
<tr>
<td>Basal DHEAS AUC</td>
<td>0.123</td>
</tr>
<tr>
<td>Post-DST DHEAS AUC*</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Note. Coef., coefficient derived from linear regression models in which the change in PTSD severity is the dependent variable and the area under the curve of the stress hormone together with the controlling variables: gender, major depressive disorder at pre-treatment and previous chronic youth trauma are the independent variables. A negative value reflects a smaller decline in PTSD severity; 95% CI, 95 percent confidence interval; AUC, Area under the curve with respect to ground; DST, Dexamethasone suppression test; DHEAS, Dehydroepiandosterone sulfate.

*Sample size slightly varied because of missing data points; DHEAS $n=20$; Post-DST DHEAS $n=21$.

*Significant at .05 level.
Dexamethasone-suppressed cortisol awakening response predicts treatment outcome in posttraumatic stress disorder

Discussion

The current study investigated whether neuroendocrine markers of PTSD predict treatment response in trauma-focused psychotherapy. The main result is that a more suppressed cortisol awakening response predicted greater PTSD symptom improvement over the course of treatment, independent of gender, the presence of MDD, and previous chronic youth trauma. Basal cortisol and DHEAS awakening responses did not significantly predict PTSD symptom change during therapy. This finding is consistent with previous studies (Olff et al., 2007; Yehuda et al., 2009) that found no differences in pre-treatment basal cortisol or DHEA levels between responders and non-responders of cognitive behavioural interventions. Our findings thus suggest that specifically the dexamethasone-suppressed cortisol awakening response is a neuroendocrine predictor for treatment success in trauma-focused psychotherapy.

These findings point to the important role of the negative feedback loop of HPA-functioning in PTSD. There are considerable inconsistencies across studies regarding lower early morning cortisol (Meewisse et al., 2007), whereas enhanced cortisol suppression after DST has been found quite consistently (de Kloet et al., 2012). Almost all findings in relation to glucocorticoid alterations in PTSD are consistent with the idea of enhanced responsiveness to glucocorticoids or increased sensitization of the glucocorticoid receptors, as demonstrated in changes in the number of glucocorticoid receptors and responsivity after dexamethasone administration (Yehuda, 2009). Our current findings indicate that patients who demonstrate this neuroendocrine profile for PTSD most clearly seem to benefit most from trauma-focused psychotherapy. In view of recent cumulating evidence of neuroendocrine alterations as pre-existing vulnerability traits for developing PTSD after trauma, it is possible that a hypersensitive stress system is a long-existing trait playing a role both in development and recovery of PTSD. However, large prospective studies would be necessary to adequately test such a hypothesis.

Possibly, cortisol treatment could also be used as intervention for PTSD. The rationale would be to restore the glucocorticoid disbalance observed in PTSD and possibly to impair the involuntary retrieval of traumatic memories. Cortisone has already been found to reduce PTSD symptoms (Aerni et al., 2004), and hydrocortisone augmentation of TF-CBT resulted in a more accelerated and ultimately greater PTSD symptom decline in a case report (Yehuda et al., 2010). Given the role of glucocorticoid receptors in both processing of traumatic memories and
psychopathology of PTSD, glucocorticoid receptor blockers can also be helpful in the treatment of PTSD (Yehuda, 2009).

A strength of the current study is the careful setup of the study as part of a randomized controlled trial with standardized treatments and independent outcome assessment. A limitation is that the number of subjects who completed the neuroendocrine measurements was small and limited the statistical power of the study. Another limitation is that the majority of patients had comorbid MDD. Although we statistically controlled for MDD, a more elegant way to disentangle the effects would have been to include separate groups. A final limitation is the lack of post-treatment neuroendocrine measurements, which could have provided information about therapy-induced changes.

In conclusion, our results point to the dexamethasone-suppressed cortisol awakening response as a biological marker for treatment success in trauma-focused psychotherapy. If replicated in larger studies, this finding may lead to treatment matching based on neuroendocrine parameters in the future.

References


Kellner, M., Muhtz, C., Peter, F., Dunker, S., Wiedemann, K., & Yassouridis, A. (2010). Increased DHEA and DHEA-S plasma levels in patients
Memory traces of trauma

Chapter 9

Dexamethasone-suppressed cortisol awakening response predicts treatment outcome in posttraumatic stress disorder


Dexamethasone-suppressed cortisol awakening response predicts treatment outcome in posttraumatic stress disorder

*PTSD: A handbook for practitioners* (pp. 399-411). New York: Guilford Press.
Chapter 10

Discussion
10.1 Overview

The aim of this thesis was to investigate important aspects of memory and information processing in patients with PTSD, and to examine therapeutic approaches for targeting traumatic memories. The following research questions were addressed:

- 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?

In this final chapter, findings of the previous chapters will be discussed. A summary of the main findings of the studies is provided, followed by the strengths and limitations of the randomized controlled trial and the cross-sectional study in disaster survivors. We further address the findings of the studies in the light of recent studies and developments, theories about PTSD, and explanations of the working mechanisms of the therapies. The chapter concludes with implications of the studies for clinical practice and recommendations for future research.

10.2 Main findings

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?

Baseline data of the randomized controlled trial provided the opportunity to compare neurocognitive performance of PTSD patients with and without MDD. Verbal memory performance proved to be significantly more impaired in PTSD patients with major depression than in PTSD patients without major depression, expressed in more impairment of learning and retrieval of separate words. No differences were found for the group with...
PTSD and MDD in the domains of verbal recognition, retrieval of a coherent paragraph, mental processing speed, shifting of attention, selective attention, or cognitive interference, compared to the group of PTSD patients without MDD. Medium-sized effects were found for group differences on verbal memory for separate words.

The cross-sectional study in disaster survivors showed that PTSD symptoms, depressive symptoms and sleep disturbances independently contributed to sustained attention performance two years after the disaster. The variables age, education, depressive symptoms and sleep disturbances all contributed to sustained attention in these disaster survivors, but correlations between PTSD symptoms and sustained attention performance were still significant for the least difficult subtests after controlling for these variables.

**What are the effects of BEP and EMDR on PTSD and its clinical correlates, and is there a difference in response pattern?**

In the randomized controlled trial, BEP and EMDR were found to be equally effective in reducing PTSD symptom severity, but speed of change was different in these psychotherapeutic treatments. Findings regarding the response pattern indicated that EMDR led to a significantly sharper decrease in PTSD symptoms than BEP. Additional analyses correcting for session duration still yielded this result. Dropout rates were similar for both treatments (29% for EMDR; 36% for BEP). Both treatments yielded large improvement effect sizes for both self-reported and clinician-rated PTSD, indicating that the majority of the participants benefitted from these treatments. The PTSD diagnosis remained present for 10% of the enrolled patients post-treatment. The treatments also had positive effects on comorbid psychiatric disorders and symptoms. MDD was present in 60% of the patients enrolled in our trial, and was diagnosed in 16% of the patients at the endpoint of our trial. Anxiety disorders other than PTSD were present in 16% of the patients before treatment, and were diagnosed in 11% of the patients at the treatment’s conclusion. Improvement effect sizes were also large for self-reported depressive and general anxiety symptoms. These effects were obtained faster in EMDR, and were similar in both treatment conditions at the endpoint.

A case report on one of the patients in the trial suggested that EMDR may also be an efficacious treatment for patients with concurrent PTSD and OCD. Successful processing of the trauma resulted in decreased anxiety when coping with trauma reminders, and subsequently decreased the need for obsessive compulsive symptoms. EMDR in this case facilitated
the application of exposure and response prevention techniques for OCD symptoms.

*Do neurocognitive disturbances in PTSD change over the course of trauma-focused psychotherapy?*

Measures of memory and executive functioning, administered both before and after treatment in the randomized controlled trial, showed significant improvements over the course of both treatments. Medium-sized improvements were found for verbal memory of a coherent paragraph. Improvements in other domains, such as verbal memory for separate words, psychomotor speed, selective attention, divided attention and cognitive interference were more modest, but also significant. Greater PTSD symptom decrease was related to better post-treatment neurocognitive performance on almost all measures, but we could not confirm any relationship between decrease of PTSD symptoms and increase in neurocognitive performance. PTSD patients with comorbid MDD improved more on cognitive interference tasks than PTSD patients without MDD. Similar neurocognitive changes were found for patients who were on serotonergic antidepressants and those who were not.

*Can predictors be identified for treatment success in trauma-focused psychotherapy? Do neuropsychological and neuroendocrine aspects of PTSD and hotspots in trauma memories contribute to treatment response?*

Verbal memory for emotionally neutral material, measured before treatment in the trial, proved to have a strong effect on treatment success. Poorer baseline performance on tasks of encoding, short-term and long-term recall of words and recall of a coherent paragraph were associated with less decrease in self-reported PTSD, for both treatment conditions. These effects were independent of baseline severity of PTSD symptoms and major depression. The strongest effects were found for delayed recall measures. Based on their pre-treatment long-term cued retrieval of words, 75.6% of the patients could be correctly classified as responder, with a sensitivity of 74.1% and a specificity of 88.9%.

From the patients who completed BEP in the trial, subgroups of the most successful and least successful treatments were selected based on their decrease in PTSD symptom severity. Subsequently, audio recordings of the imaginal exposure sessions of these treatments were assessed for the presence of hotspots and the associated emotions, cognitions, and characteristics. The mean number of hotspots did not differ between the
successful and unsuccessful treatments, but hotspots were more frequently addressed by the therapist in successful treatments. Moreover, more characteristics of hotspots, such as an audible change in affect, were present in successful treatments than in unsuccessful ones.

In another subgroup of patients, biomarkers of PTSD were investigated before their treatment in the trial with the aim of exploring their potential as a predictor for treatment success. A more suppressed cortisol curve after administration of dexamethasone significantly predicted greater PTSD decrease in trauma-focused psychotherapy, controlling for the effects of several potential mediators. Basal early morning cortisol and dehydroepiandosterone were not found to be associated with treatment outcome.

10.3 Methodological considerations: strengths and limitations

Strengths

The study had a strong design. This enabled a methodologically sound comparison of the two trauma-focused psychotherapy protocols and made it possible to study response patterns. Protocol adherence, treatment integrity checks, intention-to-treat analyses, the use of structured clinical interviews, weekly assessment of symptoms, and independent assessment of outcome contributed to the soundness of the results. A further strength of the study was the clinical relevance, taken into account by some features of a ‘practical trial’, defined as a randomized trial that combines elements of both efficacy and effectiveness designs (Schnurr, 2007). Inclusion of a heterogeneous trauma population, the cultural diversity of the sample, treatment duration dependent on patients’ recovery, and the use of non-expert therapists added to the generalizability of the results to clinical practice. This enhances the relevance of our study for making clinical decisions. Further strengths were the relatively large group of patients we included, and the administration of a wide range of predictive and outcome variables, including neurocognitive tests for verbal memory and attention, and neuroendocrine measures for a subgroup of the participants in the trial.
Limitations

Design

Limitations related to the design of the trial are mostly related to the features of effectiveness designs that we applied, which enhance generalizability but pose potential threats to internal validity. The choice to let the treatment duration depend on the patients’ recovery, as applied in clinical practice, provided a challenge for the timing of the trial’s post-assessments. We chose to schedule the first post-assessment after 6 sessions in the BEP condition and after the whole EMDR treatment, which on average was also 6 sessions. In some BEP treatments, the exposure lasted longer than the 6th session, but nevertheless the first post-assessment took place at this point in time. It is a limitation of our study that this time point was variable for EMDR but not for BEP. Also, the session duration was 30-45 minutes longer in EMDR than in BEP. Equal session durations would have allowed for a more fair comparison of the treatments. This is the reason why we performed an additional analysis to correct for session duration for the primary outcome. The session durations we implemented were standard in clinical care and were therefore applied as such. Another limitation was the allowance of concurrent treatments to a certain extent. Although our aim was to keep the pharmacological treatment as stable as possible, pharmacological treatments and changes in pharmacological treatment may have contributed to the treatment effects in a minority of the patients. Non-trauma-focused therapies may also have had an additional effect. To some extent, this may be related to the large-sized effects we found.

The primary objective of the RCT was to compare the effects of two active treatments. However, regarding the study on neurocognitive changes in response to treatment, a control group not receiving treatment would have allowed for more certainty regarding the causal role of trauma-focused psychotherapy in the improvements we found. Even though we used different versions of the neurocognitive tests pre- and post-treatment, it cannot be completely ruled out that practice effects played a role in the improvement of neurocognitive functioning over time. It was felt to be unethical to have a waitlist control group for the duration of the treatments in the study (i.e. 4 months), and thereby withholding evidence-based interventions from them for this period. Moreover, for the primary objective of the RCT to compare the effects of the treatments, it is deemed unwise to include a control group that does not account for important
factors such as therapist commitment and belief in the treatment (Bradley, Greene, Russ, Dutra, & Westen, 2005).

For the explorative studies on hotspots and neuroendocrine predictors of treatment response in various subgroups of the participants, small numbers may have led to insufficient statistical power to detect all the effects.

**Dropout from therapy and assessments**

Both treatments in the trial suffered from treatment dropout and assessment dropout. No differences were found in percentages of dropout between the treatment conditions, but 32.5% of patients did not complete the treatment they were assigned. This rate is comparable with those of other trials (Hembree et al., 2003; Schnurr et al., 2007; Schottenbauer, Glass, Arnkoff, Tendick, & Gray, 2008). Ten percent of patients dropped out before treatment, which may indicate motivational problems to start trauma therapy. Non-attendance of assessments was somewhat higher than in other trials, particularly for BEP. This non-attendance of assessments occurred more often in patients who had dropped out of treatment. Some results, for instance the neurocognitive improvements, may therefore be more reflective of changes in treatment completers.

**Generalisability**

Although the participants recruited for this trial were treatment-seeking patients at our clinic and efforts were made to maximize external validity, some selection criteria could not be avoided. This poses some limitations for the generalizability of the results. Results are therefore not necessarily representative for PTSD patients who are acutely suicidal, or who endorse diagnostic criteria for severe major depressive disorder, severe alcohol or drug dependence, lifetime psychotic disorders, and severe personality disorders. These exclusion criteria were common when the trial was started. In the mean time, there are indications that PTSD patients with a high level of borderline personality characteristics also benefit significantly from trauma-focused interventions (Feeny, Zoellner, & Foa, 2002; Clarke, Rizvi, & Resick, 2008) and stabilizing group interventions (Dorrepaal et al., 2012). Alcohol and substance related disorders do not necessarily preclude the application of trauma-focused interventions either (e.g., Hien, Campbell, Ruglass, Hu, & Killeen, 2010), nor does a chart diagnosis of psychosis (van den Berg & van der Gaag, 2012). The relatively strict exclusion criteria in the current trial may be associated with our large improvement effect sizes (Bradley et al., 2005).
**Strengths and limitations of the study in disaster survivors**

Strengths of the cross-sectional study in disaster survivors were that this was the first study to investigate sustained attention in such a population, and the participants stemmed from a community sample not necessarily seeking treatment. Limitations are that only one aspect of attention was assessed in the study, instead of multiple neurocognitive domains, and that the study may not be representative for other disaster survivors. Important characteristics of disasters (e.g., geographical location, resource loss) and survivors (e.g., age, socioeconomic status) vary and may be of influence on neuropsychological performance of survivors.

**10.4 Relevance of the findings**

*Can the feeling of safety originating from adequate memory functioning be restored by treatment? Do anxiety, depression and stress responses normalize after treatment?*

Comparing the effects of the treatments in the trial to meta-analyses (Bradley et al., 2005; Bisson et al., 2007), effect sizes of BEP are comparable to those of TF-CBT and those of EMDR are larger than in previous studies and meta-analyses. Effect sizes of BEP in our trial from pre- to post-treatment (average Cohen’s $d$ 1.75) were also somewhat larger than in other RCTs investigating BEP in comparison to waiting list or a minimal attention condition (average Cohen’s $d$ of 1.30 – 1.62, Gersons, Carlier, Lamberts, & van der Kolk, 2000; Lindauer et al., 2005; Schnyder, Müller, Maercker, & Wittmann, 2011). Both treatments also yielded large effect sizes regarding comorbid depressive symptoms and general anxiety symptoms. Only 10% of the participants in our trial kept endorsing the diagnostic criteria for a PTSD diagnosis, whereas Bradley et al. (2005) found that 33% of treatment completers and 44% of patients who entered treatment still met criteria for PTSD in their meta-analysis. Overall, the treatments investigated in our trial thus produced substantial improvements in symptomatology. However, this study did not specifically focus on the symptoms which remain after treatment, which can also lead to significant constraints in daily functioning. A study of BEP in 511 police officers who completed the treatment closely investigated the residual symptoms (Smit et al., in press). Although only 1.3% of the police officers met full criteria for PTSD post-treatment, remaining PTSD symptoms were present in almost 60% of them. Subjective concentration difficulties were the most prevalent residual symptom in 16.4 % of the police officers. This indicates that the ‘memory traces’ of trauma in sustained attention are not
gone completely should we rely on the opinion of the trauma survivor. These remaining concentration difficulties may contribute to less than optimal daily memory functioning. Also, there may be a tendency for the patients who do not get better to drop out of treatment. Our dropout analysis indeed showed that dropouts were more likely to have less symptom improvement over the first sessions of the therapy than the patients who stayed in the trial at that point. Furthermore, patients who dropped out of treatment were younger and were more likely to stem from minority ethnic groups.

In contrast with the subjective experience of concentration difficulties as a residual symptom, we found significant improvements on more objective neurocognitive tests over the course of treatment. Verbal memory for a coherent paragraph improved most from pre- to post-treatment, and verbal learning and memory for separate words, divided attention, cognitive interference, selective attention and psychomotor speed improved as well. These neuropsychological improvements are in line with changes in brain activation patterns found by other studies over the course of trauma-focused treatments. Normalized activity in the prefrontal cortex was reported after EMDR and BEP, and some studies have also found decreased limbic activation (Levin, Lazorve, & van der Kolk, 1999; Lansing, Amen, Hanks, & Rudy, 2005; Oh & Choi, 2007; Lindauer et al., 2008). In EMDR responders, increased hippocampal volumes were found (Bossini, Fagiolini, & Castrogiovanni, 2007), as well as increased posterior cingulate, anterior insula, and right parahippocampal gyrus volumes (Nardo et al., 2010). In an EEG study, Pagani et al. (2012) found a shift in cortical firing from prefrontal and limbic regions at the start of EMDR, to fusiform and visual cortex at the end of the therapy. Psychotherapy for PTSD seems to normalize the fear network in PTSD by engaging executive functions in the prefrontal cortex and thereby inhibiting emotional responses in limbic structures (LeDoux, 2002; Quide, Witteveen, El-Hage, Veltman, & Olff, 2011). A recent study by Thomaes et al. (2012) found that symptom improvement after trauma therapy also coincided with functional changes in the anterior cingulate cortex and insula when processing emotional material.

How can the differential treatment speed be explained, and which working mechanisms are involved in BEP and EMDR?

EMDR in our trial led to a significantly sharper decline in PTSD symptoms than BEP, and this effect remained after controlling for session duration in an additional analysis. As mentioned in paragraph 1.1, BEP and EMDR
target the traumatic memories in a different way and this is a likely explanation for this differential treatment effect. Detailed exposure to the memory of the trauma takes place in BEP, whereas in EMDR, short exposure moments to the hotspots in the memory of the trauma are interrupted by distracting stimulation and followed by free associations. These differences in the exposure procedure may explain why EMDR works faster. A remarkable outcome of the RCT is that the treatments lead to similar results after both interventions are finished, although they are approaching the trauma memory quite differently.

Several memory theories have offered explanations for the working mechanisms in trauma-focused interventions. A general explanation for trauma-focused psychotherapy with exposure and cognitive restructuring components comes from dual representation theory (Brewin, 2005). Brewin assumes that trauma treatment involves both the image-based memory system (SAM) and the verbal memory system. According to this theory, a form of imaginal exposure reduces re-experiencing symptoms and cognitive restructuring techniques target beliefs that the person has about him- or herself and the world. When the trauma survivor deliberately maintains attention on the content of the flashbacks, and no longer tries to avoid them, information that is only present in the SAM system is presumed to be re-encoded in the VAM system. By this process, the memories are assigned a spatial and temporal context. Trauma survivors will then be able to place their memory in the past, and to recognize that the threat is no longer present. This reduces the need for flashbacks and nightmares, and thereby leads to PTSD symptom reduction.

Another memory theory was specifically formulated to explain the effects of EMDR. This working memory account is currently the most plausible explanation for how EMDR works. It states that the eye movements offered shortly after imaginal exposure to the hotspot of the trauma tax the working memory of the trauma survivor, and thereby reduce the vividness and emotionality of the memories (Andrade, Kavanagh, & Baddeley, 1997; Gunter & Bodner, 2008; Engelhard, van Uijen, & van den Hout, 2010). It is assumed that the dual task of keeping the emotional memory in mind and performing the eye movements creates a psychological distance and leads to de-arousal, which eventually leads to PTSD symptom decrease. The eye movements task thus has an incremental value in EMDR (Lee & Cuijpers, 2013), in contrast with previous analyses and thoughts on this matter (e.g., Davidson & Parker, 2001). The working memory account is based on the multi-component model of working memory by Baddeley and colleagues (Baddeley & Hitch, 1974; Repovs &
Baddeley, 2006). Several experiments have proven that one can apply several other tasks that tax working memory instead of eye movements, such as drawing a complex figure and arithmetic assignments. This makes it likely that the component of the working memory that these tasks draw on is the central executive.

*Which factors facilitate or hinder the processing of traumatic memories and normalization of anxiety?*

Several findings of the studies in this thesis are in line with dual representation theory formulated by Brewin and colleagues (Brewin, Dalgleish, & Joseph, 1996; Brewin & Holmes, 2003). This specifically applies to factors that proved to be important for treatment success in BEP and EMDR. First, we found that several aspects of verbal memory were related to treatment outcome. The degree to which the verbal memory system is deregulated thus seems to indicate to which extent patients will be able to benefit from trauma-focused psychotherapy. Our finding of a poorer treatment response in patients with more restricted verbal memory performance led us to believe that higher-order learning and meaning-making capabilities will be limited for both emotionally neutral and trauma-related information. These underlying processes can therefore hamper the processing of trauma memories and reconsolidation. In terms of dual representation theory, this would mean that reencoding of the trauma memories from SAM into VAM and assignment of a spatial and temporal context to the memory of the trauma would not adequately take place.

Second, our explorative findings on the association between repeatedly focusing on hotspots in imaginal exposure sessions and successful treatment can be explained by dual representation theory. According to this theory, hotspots correspond to the moments where there is maximal functional separation between visuospatial and verbal processing, leading to a large discrepancy between the contents of the VAM and SAM memory systems (Brewin, 2005). Repeatedly focusing on hotspots during imaginal exposure may be necessary for successful reencoding of all potential retrieval cues into the VAM, to prevent the recurrence of flashbacks.

Apart from the above factors which can be related to dual representation theory, we also found preliminary evidence that a more flattened cortisol morning curve in response to dexamethasone was a biomarker for better treatment response to trauma-focused interventions. This points to the important role of the sensitivity of the HPA axis and the enhanced negative feedback loop in PTSD, which is one of the most
consistent neuroendocrine findings in PTSD populations. Thus, patients with the neuroendocrine picture that is most characteristic of PTSD also respond better to trauma-focused psychotherapy, whereas basal cortisol and DHEA levels do not seem to predict treatment response. This corresponds with previous research in BEP and TF-CBT (Olff, de Vries, Güzelcan, Assies, & Gersons, 2007; Yehuda et al., 2009).

In summary, we have identified some neurocognitive and neuroendocrine characteristics and autobiographical memory correlates to be associated with treatment response. These factors seem to make stronger contributions to treatment response in trauma-focused psychotherapies than certain demographic and clinical factors in our study. Previous research has already noted that demographic and clinical predictors tend to differ across populations, interventions, and outcome measures studied (Karatzias et al., 2007).

**Do the results inform us about the concept of PTSD?**

With the release of the DSM-5, it is interesting to note that the hotspots in trauma memories in our explorative pilot study were accompanied by a large proportion of emotions not present in criterion A2 of the DSM-IV. DSM A2-emotions were only present in 34% of these moments of emotional impact. Fear, helplessness, or horror in the direct aftermath of traumatic events were found to be only weak predictors of later PTSD, and other posttraumatic emotional responses, such as guilt, shame and anger, also predicted PTSD (Brewin, Andrews, & Valentine, 2000; Andrews, Brewin, Rose, & Kirk, 2000; Feeny, Zoellner, & Foa, 2000). Moreover, anger may negatively impact treatment success (Foa, Riggs, Massie, & Yarczower, 1995; Forbes, Creamer, Hawthorne, Allen, & McHugh, 2003; Forbes et al., 2008), while guilt may positively influence treatment response (Rizvi, Vogt, & Resick, 2009). Taken together, the studies mentioned here suggest that it may be a valid discussion to eliminate criterion A2 from the PTSD diagnosis in DSM-5, because a range of other emotions may be more important for who will go on to develop PTSD after a trauma. Our pilot findings on hotspots cannot contribute to the role of these emotions in the development of PTSD, but we found preliminary evidence that addressing hotspots with non DSM-IV A2 emotions is important for treatment response in trauma-focused psychotherapy. It may enhance the treatment outcome to focus on these other emotions, instead of only on fear which is now mostly the case in TF-CBT and cognitive processing therapy. Furthermore, the role of one of these emotions, anger, has been given a
more prominent position in the PTSD symptom criterion of reckless and destructive behavior expected to appear in DSM-5.

With our neurocognitive comparison study investigating PTSD patients with and without co-morbid MDD, we also hoped to contribute to the question whether PTSD with and without co-morbid MDD can be seen as separate diagnostic constructs with distinct neuropsychological profiles. Support for a somewhat more impaired verbal memory function was found in patients with PTSD + MDD, but the general neuropsychological profile was similar for both groups. Furthermore, we found some support for independent contributions of PTSD symptoms and MDD symptoms to sustained attention in disaster survivors. The evidence for distinct neuropsychological profiles is limited so far.

10.5 Clinical implications
The studies in this thesis underline treatment guidelines for PTSD (NICE, 2005; Foa, Keane, Friedman, & Cohen, 2008) that trauma-focused interventions should be the first line of treatment for patients with PTSD resulting from a single traumatic event. A history of earlier traumatic events was present in 54% of the patients, and 19% of the patients had trauma histories that can be considered ‘complex trauma’, indicating that trauma history does not need to be a reason to refrain from administration of these treatments. This study showed that BEP and EMDR both yielded large effect sizes in the reduction of PTSD symptoms, depressive symptoms and general anxiety symptoms, indicating that the majority of patients benefit from these treatments. Because both treatments were shown to be equally efficacious, with similar dropout rates and because no specific factors were shown to be differentially related to treatment outcome, we believe that patient and therapist preference can guide the choice for treatment method. Patients with a need for fast recovery from PTSD may choose for EMDR. When patients prefer more reflection on the trauma story and want to learn from the trauma, a multimodal, integrative treatment protocol such as BEP will serve them better. A general meta-analysis suggests that following patients’ preference for therapy method, format, therapist characteristics and treatment length results in better treatment outcome and less dropout (Swift, Callahan, & Vollmer, 2011).

Adhering to patient and therapist preference in the choice for a certain treatment implies that both treatments must be available in clinical settings. EMDR is widely applied and disseminated in the Netherlands and is the preferred trauma treatment for many Dutch therapists (van Minnen,
Hendriks & Olff, 2010). Less clinicians opt for TF-CBT or BEP, which may be a result of a fewer number of Dutch professionals who are trained in these treatments. Training in these therapy methods will enhance the possibility to choose this treatment option, also if the trauma survivor does not adequately recover from the first treatment that is offered. The NICE guideline (2005) advises to choose another trauma-focused intervention in case of no or only limited improvement after a specific trauma-focused intervention. Another condition for treatment of PTSD is proper identification and diagnostic assessment of PTSD patients in clinical practice. The current development of mental health care institutions to compartmentalize into departments for specific mental health problems may hinder appropriate recognition of trauma-related disorders and comorbid PTSD.

The studies in this thesis also point to the need to tailor interventions for specific groups who do not sufficiently benefit from BEP or EMDR. A first concern is the group of patients which never started treatment and the group which dropped out of treatment prematurely. Treatment dropout in our study was associated with younger age, being part of minority ethnic groups, and less symptom improvement over the first few sessions. This study was a randomized controlled trial and therefore had to strictly adhere to the treatment protocol, but in clinical practice it may be useful for these groups of patients to spend some time to build a trusting therapeutic relationship and address possible motivational problems before addressing the trauma. A second concern is the group with restricted verbal memory performance, which proved to be a strong predictor for worse treatment outcome. This is an important aspect for clinicians, as it is sometimes hard to know how much information patients ‘take home’ from the session. Administering a verbal memory test may give a more objective indication of the difficulties the patient experiences in this domain. In the future, it would be good to develop a kind of ‘mini mental state examination’ for verbal memory in PTSD patients, because memory performance varies considerably among these patients. For the people who do not sufficiently benefit from treatment, alternative or augmented treatments need to be evaluated and treatment parameters like treatment length need to be varied (Schnyder, 2005; Bradley et al., 2005). Visual memory is generally less impaired in PTSD than verbal memory (Brewin, Kleiner, Vasterling, & Field, 2007), so visual enhancers to the therapy can be useful. Other possibilities include adjusting the pace and complexity of treatment, applying a more graduated approach for trauma recall, and providing reminders of the session content and homework (Brewin, 2005).
For the therapist, this may also mean that ‘hotspots’ need to be addressed repeatedly in BEP treatments. Another point of attention for the therapists may be to look for hotspots characteristics in imaginal exposure, to ensure that sufficient emotional engagement with the trauma memory takes place in BEP.

### 10.6 Future research

Regarding the effects of the treatments, one question that remains to be answered is the long term follow-up effect. The last assessment point in our trial was 12 months after the second post-assessment, and results from this assessment will follow in the near future. Few randomized studies, however, have collected data beyond that time point so the long term effects are not yet entirely clear. These data would provide information about resilience in the face of other traumatic events or life events. In addition, cost-effectiveness of the treatments deserves further study.

An important question for future research is how dropout can be minimized and treatment results maximized, in order to be able to offer more efficacious treatments to PTSD patients. Optimal session duration and frequency should be investigated. Good results have been obtained with an intensive one week treatment program, including trauma-focused interventions, for the treatment of PTSD (Ehlers et al., 2010; Hendriks, de Kleine, van Rees, Bult & van Minnen, 2010). At our clinic we have had positive experiences applying a 7-work day intensive trauma treatment program for patients with PTSD and severe comorbid conditions such as OCD. These interventions show potential and should be studied further. A related topic is at which time point interventions should be offered in order to maximize efficacy. Possibly, trauma-focused acute interventions can be helpful to prevent PTSD in the long run. Preliminary positive results have been found for a brief form of trauma-focused CBT (Rothbaum et al., 2012). The efficacy of a brief EMDR intervention applied in the acute aftermath of trauma to prevent PTSD in the long run remains to be studied.

Several topics regarding memory and neurocognitive performance are worth further investigation. In our trial we found an association between verbal memory performance and treatment outcome, but other neurocognitive variables could be related to treatment response. In light of the working memory hypothesis described earlier in this chapter, Gunter and Bodner (2008) have shown that more restricted reading span, which is a measure of executive functioning, is related to better treatment outcome in an EMDR-like procedure in students. Further research is needed to...
replicate this finding in PTSD patients since it can be assumed that their working memory is more ‘taxed’ with flashbacks of traumatic events. Similarly, it is necessary to replicate findings regarding distracting tasks used in EMDR experiments in patients during the whole EMDR treatment. It could be expected that eye movements are more effective in reducing the vividness and emotionality than listening to beeps (cf. van den Hout et al., 2011; 2012). It would be interesting to compare the predictive effects of verbal versus visual memory in response to trauma-focused psychotherapy. Visual memory is less impaired in PTSD, so a weaker or absent association between verbal memory and treatment success would provide support for the dual representation theory.

In the cross-sectional study on sustained attention, subjective sleep disturbances were found to be related to sustained attention performance. It is likely that sleep disturbances affect verbal memory in PTSD patients. However, discrepancies are often found between subjective reports of sleep and objective sleep quality measured by polysomnography in PTSD (van Liempt, 2012). Relationships between objective sleep parameters and neurocognitive functioning are currently under investigation in veterans and police officers with and without PTSD as part of a collaboration between the Academic Medical Center, the University of Amsterdam, and Arq Psychotrauma Expert Group.

Findings on hotspots and HPA functioning in relation to treatment outcome in this thesis are preliminary because they were sought in subsamples of the larger trial. Replication of these findings in a larger sample is much encouraged. More statistical power would possibly allow for finding more biomarkers of treatment response. Assessment of the sensitivity of the HPA-axis by means of the dexamethasone suppression test before and after trauma-focused treatment can enhance our understanding of improved neuroendocrine functioning in response to treatment. Taken together, the proposed studies will further clarify if trauma survivors with PTSD may be able to place the psychological, neurocognitive and physiological distress, or the ‘memory traces of trauma’, in the past after treatment.

References


---

Memory traces of trauma


---

**Memory traces of trauma**

173

Summary

In the Netherlands, 81% of the general population experiences at least one potentially traumatic event in their life and the lifetime prevalence of posttraumatic stress disorder (PTSD) is around 7%. The diagnostic criteria for PTSD in the Diagnostic and Statistical Manual of Mental Disorders, fourth and fifth edition, include symptoms that are directly connected with memory, such as recurrent, involuntary and intrusive memories, inability to recall key features of the trauma, problems in concentration, increased attention for danger and hypervigilance. This thesis is about the “traces” engraved by a traumatic experience in memory when the trauma survivor has developed PTSD. Certain details of the traumatic experience, such as the rifle of a gun, are remembered extensively by these survivors and may continue to show up in their mind 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 during the trauma. Because of the continued focus on danger even when the danger is no longer there, less capacity is available for daily tasks that require memory functioning and concentration in trauma survivors with PTSD.

In the introduction to this thesis (Chapter 1), the current knowledge about the ‘memory traces of trauma’ is described. In PTSD, the memory of the trauma is linked to psychological and physiological responses that resemble the response of the survivor when being faced with the trauma. The prolonged stress responses that accompany PTSD may be associated with changes in hypothalamic-pituitary-adrenal-axis (HPA-axis) functioning. Several HPA-axis alterations have been reported in PTSD populations, including lower basal cortisol values and enhanced sensitivity of the stress response system. Information about danger has priority for survival, and is thus processed preferentially. The moments with the greatest emotional impact, also called ‘hotspots’, are reappearing in the mind of the trauma survivor with PTSD in the form of nightmares or intrusions. Less capacity is available for processing emotionally neutral material in PTSD, resulting in decreased memory performance for verbal material and executive functioning. Currently, the most effective interventions for alleviating PTSD are trauma-focused cognitive behavioural therapy (TF-CBT) and Eye Movement Desensitization and Reprocessing therapy (EMDR). These
therapies could also be called ‘memory-focused’ interventions because patient and therapist work with the memory of the trauma. The most prominent difference between these approaches is that TF-CBT requires a very detailed imaginal exposure to the traumatic event, whereas the imaginal exposure in EMDR is limited and interrupted by free associations and a distracting task (such as performing eye movements). Brief Eclectic Psychotherapy (BEP) is seen as a cognitive behavioural intervention in leading treatment guidelines, because its treatment components overlap most with this approach. This treatment includes detailed imaginal exposure to the traumatic event, as well as psycho-education, writing assignments, meaning-making, mementos of the trauma, and a farewell ritual. No well-powered studies so far 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. Therefore, we conducted a randomized controlled trial to compare these treatments and study neurocognitive and neurobiological processes in relationship to treatment outcome.

Neuropsychological impairments in PTSD in the domains of attention, memory and executive functions can be related to several mental health symptoms and disorders that are frequently present in trauma survivors and PTSD patients. In chapter 2 and chapter 3, we tried to disentangle the contributions of PTSD and various co-morbid conditions to the neuropsychological performance of trauma survivors and PTSD patients. In chapter 2, our aim was to compare 84 PTSD patients with a comorbid major depressive disorder (MDD) to 56 PTSD patients without major depressive disorder to find out if they differed in terms of their performance on tasks of verbal memory and executive functioning. Baseline neuropsychological test data of the randomized controlled trial we conducted provided the opportunity to do so. Verbal memory performance proved to be significantly more impaired in PTSD patients with major depression than in PTSD patients without major depression, expressed in more impairment of learning and recall of separate words. No differences were found for the group with PTSD and MDD in the domains of verbal recognition, retrieval of a coherent paragraph, mental processing speed, shifting of attention, selective attention, or cognitive interference, compared to the group of PTSD patients without MDD. Medium-sized differences between the groups were found in verbal memory for separate words.

In chapter 3, a cross-sectional study is described on sustained attention in 135 disaster survivors who experienced the fireworks disaster.
Summary and Appendix

in Enschede, The Netherlands, 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 test. Our aim here was to investigate the extent to which sustained attention performance was related to PTSD symptoms, depressive symptoms and sleep disturbances. Results of this study showed that self-reported PTSD symptoms, depressive symptoms and sleep disturbances independently contributed to sustained attention performance two years after the disaster. The variables age, education, depressive symptoms and sleep disturbances all contributed to sustained attention in these disaster survivors. Partial correlations between PTSD symptoms and sustained attention performance were still significant for the least difficult subtests after controlling for depressive symptomatology and sleep disturbances. We concluded from these studies that there is some evidence for separate contributions of PTSD symptoms and frequently co-morbid symptoms and disorders to neurocognitive performance of trauma survivors and PTSD patients.

Sufficiently large randomized controlled trials are recommended by PTSD treatment guidelines to provide more evidence on the effectiveness of the various therapies and to increase our knowledge about the types of treatment and duration of treatment that are efficacious. Chapter 4 describes the main results of the randomized controlled trial that compared BEP and EMDR efficacy and response patterns. We included 140 adult outpatients with PTSD and randomly assigned them to either BEP or EMDR. Both EMDR and BEP were carried out according to treatment manuals and administered as in clinical practice, allowing for the number of sessions to vary depending on recovery. Self-reported PTSD symptoms were the primary outcome of the trial and were assessed at all treatment sessions and assessments. Clinician-rated PTSD, co-morbid psychiatric conditions, self-reported depression and general anxiety were secondary outcomes in this trial. These were assessed pre-treatment, at mid-term in a first post-assessment, and at the endpoint (second post-assessment). The first post-assessment took place after the exposure phase of BEP and after the whole EMDR treatment. Patients received an average number of 6.5 EMDR sessions of 90 minutes or 14.7 BEP sessions of 45-60 minutes in the trial. BEP and EMDR were found to be equally effective in reducing PTSD symptom severity, but the pace of the symptom decline was different in these treatments. Findings regarding the response pattern indicated that EMDR led to a significantly faster decrease in PTSD symptoms than BEP.
Additional analyses correcting for session duration still yielded this result. Dropout rates were similar for both treatments (29% for EMDR; 36% for BEP). Both treatments yielded large improvement effect sizes for both self-reported and clinician-rated PTSD, indicating that the majority of the participants benefitted from these treatments. The PTSD diagnosis remained present for 10% of the enrolled patients post-treatment. The treatments also had positive effects on co-morbid psychiatric disorders and symptoms. Clinician-rated MDD was present in 60% of the patients enrolled in our trial, and was diagnosed in 16% of the patients at the endpoint of our trial. Clinician-rated anxiety disorders other than PTSD were present in 16% of the patients before treatment, and were diagnosed in 11% of the patients at the treatment’s conclusion. Large improvement effect sizes were found for self-reported depressive and general anxiety symptoms. These effects were obtained faster in EMDR, but were similar in both treatment conditions at the endpoint.

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 explores the therapeutic mechanisms involved in treatment of these often co-occurring conditions. The case report suggested that EMDR may be an efficacious treatment for patients with concurrent PTSD and OCD. For this patient, successful processing of the trauma resulted in decreased anxiety when coping with trauma reminders, and subsequently decreased the need for obsessive compulsive symptoms. EMDR facilitated the application of exposure and response prevention techniques for OCD symptoms and shortened the treatment trajectory in this case.

In chapter 6, verbal memory and executive functioning are examined over the course of trauma-focused psychotherapy in the randomized controlled trial. This part of the study investigated if changes in neuropsychological functioning were present over the course of BEP and EMDR in 88 participants who completed neuropsychological assessments pre- and post-treatment. Measures of memory and executive functioning showed significant improvements over the course of both treatments. The magnitude of these effects did not differ between treatments. Medium-sized improvements were found for verbal memory of a coherent paragraph. Improvements in other domains, such as verbal memory for separate words, psychomotor speed, selective attention, divided attention and cognitive interference were more modest, but also statistically
significant. PTSD patients with co-morbid MDD improved more on cognitive interference tasks than PTSD patients without MDD. Similar neurocognitive changes were found for patients who were on serotonergic antidepressants and those who were not. We concluded that neurocognitive deficits in PTSD can improve over the course of trauma-focused psychotherapy and are therefore at least partly reversible. The benefits in terms of PTSD symptom reduction during the course of treatment seem to translate into enhanced neurocognitive performance after treatment.

With the aim of determining which treatment works best for whom, several potential predictors were investigated in relationship to treatment outcome among participants of the randomized controlled trial. Chapter 7 investigates the association between baseline verbal memory performance and decrease in self-reported PTSD symptoms during BEP and EMDR. In this part of the study we also investigated if we could correctly classify patients as treatment responder based on their pre-treatment memory performance. Verbal memory for emotionally neutral material, measured before treatment in the trial, proved to have strong effects on treatment success. Poorer baseline performance on tasks of encoding, short-term and long-term recall of words and recall of a coherent paragraph were associated with less decrease in self-reported PTSD symptoms for both treatment conditions. These effects were independent of baseline severity of PTSD symptoms and major depression. The strongest effects were found for delayed recall measures. Based on their pre-treatment long-term cued recall of words, 75.6% of the patients could be correctly classified as responder, with a sensitivity of 74.1% and a specificity of 88.9%. We concluded that the more attenuated verbal memory performance is in PTSD patients, the less likely they are to benefit from trauma-focused psychotherapy. Memory measures may give an indication to clinicians who will benefit from treatment, and who will not.

In chapter 8, a pilot study on the moments of the trauma story with the greatest emotional impact (hotspots) is described in relationship to treatment outcome in BEP therapy. In this pilot, hotspots in imaginal exposure sessions were coded in 10 successful and 10 unsuccessful BEP treatments according to a manual. Subgroups of the most successful and least successful treatments were formed based on participants’ decrease in self-reported PTSD symptom severity. Audio recordings of the imaginal exposure sessions of these treatments were assessed for the presence of hotspots and the associated emotions, cognitions, and characteristics. The
mean number of hotspots did not differ between the successful and unsuccessful treatments, but hotspots were more frequently addressed by the therapist in successful treatments (as compared to unsuccessful ones). Moreover, more characteristics of hotspots, such as an audible change in affect, were present in successful treatments than in unsuccessful ones. Although we cannot draw causal inferences from this study, we concluded that it seems important for successful therapy to repeatedly address the most difficult moments of the trauma memory, and to observe characteristics of hotspots during imaginal exposure. This may not only be important in BEP, but also in other trauma-focused psychotherapies.

In chapter 9, HPA-axis functioning was examined in relationship to treatment outcome in a subsample of 24 participants of the randomized controlled trial. Previously established biomarkers of PTSD were investigated in saliva samples during two consecutive days before their treatment in the trial with the aim of exploring their potential as a predictor for treatment success. The sensitivity of the stress system was tested by the administration of a low dose of dexamethasone at the end of the first day of saliva sampling. A more suppressed cortisol curve after administration of dexamethasone significantly predicted greater self-reported PTSD symptom decrease in trauma-focused psychotherapy, controlling for the effects of several potential mediators of HPA-axis functioning. Basal early morning cortisol and dehydroepiandosterone were not found to be associated with treatment outcome, confirming results of previous studies. These findings highlight the important role of the negative feedback loop of the HPA-axis in PTSD.

In chapter 10, we discussed the results of the research described in the previous chapters and described the implications for clinical practice. In line with several treatment guidelines and based on our findings that both treatments yielded large effect sizes, we recommend that trauma-focused psychotherapies should be the first line of treatment for patients with PTSD resulting from a single traumatic event. Because BEP and EMDR were shown to be equally efficacious, had similar dropout rates and because no specific factors were shown to be differentially related to treatment outcome, we believe that patient and therapist preference can guide the choice for treatment method. Patients with a need for fast recovery from PTSD may choose EMDR. When patients prefer more reflection on the trauma story and want to learn from the trauma, a multimodal, integrative treatment protocol such as BEP will probably serve them better.
Neurocognitive and neurobiological variables and their relationship to treatment processes have the potential to enhance our knowledge about treatment of PTSD. Verbal memory and executive functioning significantly improved over the course of trauma-focused psychotherapy in the trial. Especially verbal memory measures can be valuable indicators for who will benefit from trauma-focused treatment. Our findings on pre-treatment HPA-axis functioning and hotspots in relationship to treatment success need to be replicated in larger trials, but potentially have important implications for clinical practice. We suggest that future research should investigate how to minimize dropout from treatment and at tailoring interventions for subgroups of PTSD patients which benefit less from trauma-focused psychotherapy, such as patients who performed worse on pre-treatment verbal memory in our trial. Finally, knowing more about optimal timing of the interventions, as well as examining optimal session duration and frequency will contribute to more efficacious treatments for PTSD patients in the future.
Samenvatting

In Nederland maakt 81% van de algemene bevolking tenminste een traumatische gebeurtenis mee gedurende het leven en de levensloopprevalentie van de posttraumatische stress stoornis (PTSS) is ongeveer 7%. De diagnostische criteria voor PTSS in het handboek voor psychische stoornissen, de Diagnostic and Statistical Manual of Mental Disorders, vierde en vijfde editie, omvatten symptomen die rechtstreeks verband houden met het geheugen. De in dit kader genoemde symptomen zijn terugkerende, onvrijwillige en opdringerige herinneringen, het onvermogen om belangrijke aspecten van het trauma te herinneren, concentratieproblemen, toegenomen aandacht voor gevaar en verhoogde waakzaamheid. Dit proefschrift gaat over de "sporen" die een traumatische ervaring in het geheugen heeft gegraveerd als iemand PTSS heeft ontwikkeld. Bepaalde details van de traumatische ervaring, zoals de loop van een pistool, worden zeer scherp onthouden door getroffenen van trauma's en kunnen blijven opkomen in hun hoofd in de vorm van flashbacks en nachtmerries, vergezeld van heftige emoties. Andere details lijken minder prioriteit hebben in de informatieverwerking en worden gemakkelijk vergeten, zoals de volgorde waarin de gebeurtenissen tijdens het trauma plaatsvonden. Vanwege de voortdurende focus op gevaar, zelfs wanneer het gevaar objectief geweken is, is er bij getroffenen met PTSS minder capaciteit beschikbaar voor dagelijkse taken die een beroep doen op geheugen en concentratie.

In de inleiding van dit proefschrift (hoofdstuk 1), wordt de huidige kennis over de 'geheugensporen van trauma' beschreven. Bij PTSS is de herinnering aan het trauma gekoppeld aan psychologische en fysiologische reacties die lijken op de reactie van de getroffene toen men het trauma meemaakte. De langdurige stressreacties die gepaard gaan met PTSS zijn geassocieerd met verschillende veranderingen in het functioneren van de hypothalamus-hypofyse-bijnier-as (HHB-as). Studies hebben verscheidene veranderingen in de HHB-as vastgesteld bij groepen mensen met PTSS, waaronder lagere basale cortisol waarden en een versterkte gevoeligheid van het stress-systeem. Informatie over gevaar is belangrijk voor de overleving en heeft daarom een voorkeurspositie in de informatieverwerking. De momenten van het trauma met de grootste emotionele impact, ook wel 'hotspots' genoemd, blijven terugkomen in de
Summary and Appendix

vorm van nachtmerries of flashbacks bij getroffenen met PTSS. Er is minder capaciteit beschikbaar voor het verwerken van emotioneel neutraal materiaal bij PTSS, wat resulteert in verminderd geheugen voor verbaal materiaal en verminderde executieve functies. Momenteel zijn de meest effectieve interventies voor het behandelen van PTSS Traumagerichte Cognitieve Gedragstherapie (TG-CGT) en Eye Movement Desensitization and Reprocessing therapie (EMDR). Deze therapiën kunnen ook ‘geheugen-gerichte’ interventies worden genoemd, omdat patiënt en therapeut werken met de herinnering aan het trauma. Het meest opvallende verschil tussen deze benaderingen is dat TG-CGT een zeer gedetailleerde imaginaire blootstelling aan de traumatische gebeurtenis vereist, terwijl de imaginaire blootstelling in EMDR beperkt is en onderbroken wordt door vrije associaties en een afleidende taak (zoals het uitvoeren van oogbewegingen). Beknopte Eclectische Psychotherapie (BEP) wordt gezien als een cognitief gedragstherapeutische interventie in de leidende therapierrichtlijnen, omdat de componenten het meeste overlappen met deze aanpak. Deze behandeling omvat gedetailleerde imaginaire blootstelling aan de traumatische gebeurtenis, psycho-educatie, schrijfopdrachten, betekenisgeving, memorabilia en een afscheidsritueel. Er zijn echter nog geen studies met voldoende statistische power verricht waarin EMDR rechtstreeks met BEP werd vergeleken, noch is het responspatroon onderzocht om vast te stellen of de ene therapie efficiënter is in het behandelen van de traumatische herinneringen dan de andere. We hebben daarom een gerandomiseerde effectstudie verricht om deze behandelingen te vergelijken en neurocognitieve en neurobiologische processen in relatie tot behandelresultaat te onderzoeken.

Neuropsychologische verslechteringen bij PTSS op het gebied van aandacht, geheugen en executieve functies kunnen gerelateerd zijn aan verschillende psychische klachten en stoornissen die vaak co-morbid aanwezig zijn bij getroffenen van trauma’s en bij PTSS patiënten. In hoofdstuk 2 en hoofdstuk 3 probeerden we de specifieke bijdragen van PTSS en verschillende co-morbid stoornissen aan de neuropsychologische prestaties vast te stellen bij getroffenen en PTSS patiënten. In hoofdstuk 2 was ons doel om 84 PTSS patiënten mét een co-morbid depressieve stoornis te vergelijken met 56 PTSS patiënten zonder depressieve stoornis om er achter te komen of er verschillen waren in hun prestaties op verbale geheuventaken en executieve functietaken. Baseline data van de neuropsychologische tests in de gerandomiseerde trial maakten het mogelijk om dit te doen. Verbale geheugenprestaties bleken...
significant meer verslechterd te zijn bij PTSS patiënten met een depressieve stoornis dan bij PTSS patiënten zonder depressieve stoornis, wat tot uiting kwam in een significant slechtere prestatie bij het opslaan en ophalen van afzonderlijke woorden. Er werden geen verschillen gevonden voor de groep patiënten met PTSS en depressie op de domeinen verbale recognitie, het oproepen van een coherent verhaal, mentale verwerkingssnelheid, verdeelde aandacht, selectieve aandacht en cognitieve interferentie, in vergelijking met de groep patiënten met PTSS zonder depressie. Er werden middelgrote effectgroottes gevonden voor de verschillen tussen de groepen met betrekking tot het verbale geheugen voor afzonderlijke woorden.

In **hoofdstuk 3** wordt een cross-sectionele studie beschreven naar volgehouden aandacht bij 135 getroffenen van een ramp die de vuurwerkramp in Enschede op 13 mei 2000 hadden meegemaakt. Twee jaar na de ramp werden bij deelnemers gestructureerde klinische interviews en vragenlijsten afgenoem en werd volgehouden aandacht gemeten met behulp van neuropsychologische test. Het doel daarvan was om te onderzoeken in welke mate volgehouden aandachtsprestaties verklaard konden worden door PTSS symptomen, depressieve symptomen en slaapstoornissen. Resultaten van deze studie lieten zien dat zelfgerapporteerde PTSS symptomen, depressieve symptomen en slaapstoornissen een onafhankelijke bijdrage leverden aan volgehouden aandachtsprestaties twee jaar na de ramp. De variabelen leeftijd, opleiding, depressieve symptomen en slaapstoornissen droegen allen bij aan de volgehouden aandacht bij de getroffenen. Partiële correlaties tussen PTSS symptomen en volgehouden aandachtsprestaties bleven significant voor de minst moeilijke subtests na controle voor depressieve symptomen en slaapstoornissen. Uit deze studies concludeerden we dat er enig bewijs is voor afzonderlijke bijdragen van PTSS symptomen en veel voorkomende co-morbide symptomen en aandoeningen aan de neurocognitieve prestaties van getroffenen van trauma’s en PTSS patiënten.

Richtlijnen voor de behandeling van PTSS bevelen gerandomiseerde trials van voldoende grootte aan om meer evidence te verzamelen over de effectiviteit van de verschillende therapieën en onze kennis te vergroten van de behandelmethoden en -duur die het meest doeltreffend zijn. **Hoofdstuk 4** beschrijft de belangrijkste resultaten van de gerandomiseerde gecontroleerde trial die de effectiviteit en het responspatroon van BEP en EMDR vergeleek. In deze trial werden 140 volwassen ambulante patiënten met PTSS geïncludeerd en willekeurig toegewezen aan BEP of EMDR. EMDR en BEP werden uitgevoerd volgens protocol en toegepast zoals in de
klinische praktijk, waardoor het aantal sessies varieerde afhankelijk van het herstel. Zelf-gerapporteerde PTSS symptomen waren de primaire uitkomstmaat en werden gemeten tijdens alle behandelsessies en metingen. PTSS zoals gemeten met het gestructureerde klinische interview, co-morbide psychiatrische stoornissen, zelfgerapporteerde depressie en algemene angstsymptomen waren de secundaire uitkomstmaten. Deze werden gemeten voor de behandeling, halverwege bij een eerste nameting, en bij het eindpunt (tweede nameting). De eerste nameting vond plaats na de exposure fase van BEP en na de hele EMDR behandeling. Patiënten kregen gemiddeld 6.5 EMDR sessies van 90 minuten of 14.7 BEP sessies van 45 tot 60 minuten in de studie. BEP en EMDR bleken even effectief te zijn in het verminderen van zelfgerapporteerde PTSS symptomen, maar de snelheid waarmee deze daling werd bereikt verschilde. Met betrekking tot het responspatroon werd gevonden dat EMDR tot een significant snellere daling van PTSS symptomen leidde dan BEP. Bij analyses waarbij gecorrigeerd werd voor de duur van de sessies bleef dit resultaat overeind. De dropout percentages waren gelijk voor beide behandelingen (29% voor EMDR; 36% voor BEP). Beide behandelingen leidden tot grote effecten voor zowel zelfgerapporteerde PTSS symptomen als PTSS zoals vastgesteld in het gestructureerd klinisch interview, wat aangeeft dat de meerderheid van de deelnemers profiteerde van deze behandelingen. De diagnose PTSS bleef aanwezig bij 10% van de patiënten na behandeling. De behandelingen hadden ook positieve effecten op co-morbide psychische stoornissen en symptomen. Een depressieve stoornis, gediagnosticeerd met een klinisch interview, werd vastgesteld bij 60% van de patiënten die werden geïncludeerd in de studie en was aanwezig bij 16% van de patiënten bij de tweede nameting. Angststoornissen anders dan PTSS, gemeten met een klinisch interview, waren aanwezig bij 16% van de patiënten vóór de behandeling, en werden gediagnosticeerd bij 11% van de patiënten bij de tweede nameting. De grote effecten werden ook gevonden voor zelfgerapporteerde depressieve en algemene angstsymptomen. Deze effecten werden sneller bereikt bij EMDR, maar waren gelijk bij beide behandelcondities aan het eind.

Hoofdstuk 5 is een case report van één van de patiënten uit de studie die gediagnosticeerd was met PTSS en obsessief-compulsieve stoornis (OCS). Dit artikel zoomt in op het verhaal van de patiënt, het meegemaakt trauma en zijn behandeling om de therapeutische mechanismen die betrokken zijn bij de behandeling van deze vaak samen voorkomende diagnoses te onderzoeken. Het case report suggereert dat EMDR een
effectieve behandeling kan zijn voor patiënten met PTSS en co-morbide OCS. Bij deze patiënt leidde succesvolle verwerking van het trauma tot verminderde angst bij triggers van de traumatische herinneringen, waarmee de reden voor de obsessieve compulsieve symptomen verdween. EMDR vergemakkelijkte de toepassing van exposure en responspreventietechnieken voor OCS en verkortte het behandeltraject van deze patiënt.

In hoofdstuk 6 werden verbale geheugentaken en executieve functietaken onderzocht gedurende traumagerichte psychotherapie in de gerandomiseerde trial. Dit deel van de studie onderzocht of er veranderingen konden worden vastgesteld in neuropsychologisch functioneren in de loop van BEP en EMDR bij de 88 deelnemers van de gerandomiseerde trial die de neuropsychologische metingen voor en na de behandeling voltooiden. De geheugentests en executieve functietests lieten significante verbeteringen zien in de loop van beide behandelingen. De omvang van deze effecten verschilde niet van elkaar voor de twee behandelcondities. Er werden middelgrote verbeteringen gevonden voor verbaal geheugen voor een coherent verhaal. Verbeteringen op de andere domeinen, zoals verbaal geheugen voor afzonderlijke woorden, psychomotorische snelheid, selectieve aandacht, verdeelde aandacht en cognitieve interferentie waren bescheiden, maar ook statistisch significant. PTSS patiënten met co-morbide depressieve stoornis verbeterden meer op cognitieve interferentietaken dan PTSS patiënten zonder depressie. Er werden geen verschillen gevonden in neurocognitieve verbetering tussen patiënten die waren ingesteld op serotonerge antidepressiva en degenen die deze medicatie niet kregen. Wij concludeerden dat neurocognitieve verslechteringen bij PTSS in de loop van de traumagerichte psychotherapie kunnen verbeteren en daarmee ten minste gedeeltelijk omkeerbaar zijn. De winst die in de loop van de behandeling geboekt wordt in termen van vermindering van de PTSS symptomen lijkt zich te vertalen in verbeterde neurocognitieve prestaties na de behandeling.

Om te bepalen welke behandeling het beste werkt voor wie werden er verschillende potentiële voorspellers onderzocht in relatie tot behandelresultaat bij de deelnemers van de gerandomiseerde gecontroleerde trial. In hoofdstuk 7 werd de relatie tussen verbaal geheugen voor aanvang van de behandeling en afname van zelfgerapporteerde PTSS symptomen tijdens BEP en EMDR onderzocht. In
dit deel van de studie onderzochten we ook of we patiënten correct als ‘responder’ konden classificeren op basis van hun geheugenprestaties voor de behandeling. Verbaal geheugen voor emotioneel neutraal materiaal, gemeten voor de behandeling in de trial, bleek sterk effecten te hebben op behandel succes. Slechtere prestaties op taken waarbij woorden ingeprent moesten worden in het geheugen, alsmede taken waarbij deze woorden op korte termijn en lange termijn moesten worden opgeroepen uit het geheugen en het oproepen van een coherent verhaal waren gerelateerd aan minder verbetering van de zelfgerapporteerde PTSS symptomen voor beide behandelingen. Deze effecten waren onafhankelijk van de ernst van de PTSS symptomen en depressieve symptomen voor de behandeling. De sterkste effecten werden gevonden voor de uitgestelde herinneringstaken. Op basis van de prestaties op een uitgestelde herinneringstaak waarbij met aanwijzingen woorden moesten worden opgehaald uit het geheugen (cued recall), kon 75.6% van de patiënten correct worden geclassificeerd als res perder, met een sensitiviteit van 74,1% en een specificiteit van 88,9%. Concluderend kunnen we stellen dat hoe slechter de verbale geheugenprestaties bij patiënten van PTSS vóór de behandeling zijn, des te kleiner de kans is dat iemand zal profiteren van traumagerichte psychotherapie. Geheugentests kunnen een indicatie geven wie van de patiënten zal profiteren van de behandeling, en wie niet.

In hoofdstuk 8 wordt een pilotstudie beschreven die de momenten van de traumaverhalen met de grootste emotionele impact (hotspots) in kaart brengt in relatie tot behandelresultaat bij BEP. In deze pilot werden hotspots met behulp van een handleiding gecodeerd bij imaginaire exposure sessies van 10 succesvolle en 10 niet succesvolle BEP behandelingen. De subgroepen met de meest succesvolle en minst succesvolle behandelingen werden gevormd op basis van de afname van de zelfgerapporteerde PTSS symptomen. Audio opnames van de imaginaire exposure sessies werden beoordeeld op de aanwezigheid van hotspots en de bijbehorende emoties, cognities en kenmerken van hotspots. Er was geen verschil in het gemiddelde aantal hotspots tussen de geslaagde en niet geslaagde behandelingen, maar de therapeut liet hotspots vaker aan de orde komen in de exposure bij succesvolle behandelingen (in vergelijking met de niet succesvolle behandelingen). Bovendien waren er meer kenmerken van hotspots, bijvoorbeeld een hoorbare verandering in affect, aanwezig bij succesvolle behandelingen dan bij niet succesvolle. Hoewel we geen causale conclusies uit deze studie kunnen trekken, concludeerden we dat het belangrijk lijkt te zijn voor succesvolle behandeling om de
moeilijkste momenten van het trauma herhaaldelijk aan de orde te laten komen en te letten op kenmerken van hotspots tijdens de imaginaire exposure. Dit is mogelijk niet alleen belangrijk bij BEP, maar ook bij andere vormen van traumagerichte psychotherapie.

In hoofdstuk 9 werd de werking van de HHB-as onderzocht in relatie tot behandelresultaat in een subgroep van 24 deelnemers van de gerandomiseerde trial. PTSS biomarkers werden onderzocht in speekselmonsters gedurende twee opeenvolgende dagen vóór de behandeling in de trial om te exploreren of dit behandelresultaat zou kunnen voorspellen. De gevoeligheid van het stress-systeem werd getest door toediening van een lage dosis dexamethason aan het einde van de eerste dag van de speekselmonsters. Een vlakkere cortisolcurve na toediening van de dexamethason bleek een significante voorspeller te zijn voor een grotere afname van de zelfgerapporteerde PTSS symptomen bij traumagerichte psychotherapie. Hierbij werd gecontroleerd voor de invloed van verschillende mogelijk mediërende factoren op de HHB-as. De basale cortisolwaardes in de periode na het wakker worden en de ochtendwaarden van een ander stresshormoon, dehydroepiandosteron, bleken geen relatie te vertonen met het resultaat van de behandeling, wat een bevestiging was van de resultaten van eerdere studies. Deze bevindingen wijzen op de belangrijke rol van de negatieve feedback loop van de HHB-as bij PTSS.

In hoofdstuk 10 bespraken we de resultaten van het onderzoek zoals in de vorige hoofdstukken beschreven en gingen we in op de gevolgen voor de klinische praktijk. In overeenstemming met verschillende behandelrichtlijnen en op basis van onze bevinding dat beide behandelingen grote effectgroottes hadden, raadden we traumagerichte psychotherapie aan als eerste keus behandeling voor patiënten met PTSS als gevolg van een enkelvoudige traumatische gebeurtenis. Omdat BEP en EMDR even effectief bleken te zijn, de dropout niet significant verschilde en omdat we geen specifieke voorspellende factoren hebben gevonden voor behandelresultaat bij een van beide behandelingen zijn we van mening dat de voorkeur van patiënt en therapeut gevolgd kan worden in de keuze voor een van beide behandelmethoed. Patiënten met behoefte aan snel herstel van hun PTSS kunnen voor EMDR kiezen. Wanneer patiënten meer reflectie op het traumaverhaal prefereren en willen leren van het trauma, zal een multimodale, integratieve behandeling zoals BEP waarschijnlijk meer passend zijn. Neurocognitieve en neurobiologische variabelen en hun
relatie tot behandelprocessen kunnen onze kennis over de behandeling van PTSS vergroten. Tests voor verbaal geheugen en executieve functies lieten significante verbeteringen zien in de loop van traumagerichte psychotherapie. Met name verbale geheugentests kunnen waardevolle indicatoren zijn voor wie van traumagerichte behandeling zal profiteren. Onze bevindingen over de relatie tussen het functioneren van de HHB-as en hotspots in relatie tot behandelsucces vragen om replicatie in grotere studies, maar hebben in potentie belangrijke gevolgen voor de klinische praktijk. Wij stellen dat toekomstig onderzoek dropout bij behandeling zou moeten minimaliseren, en zich zou moeten richten op het afstemmen van behandelingen op subgroepen van PTSS patiënten die minder profiteren van traumagerichte psychotherapie, zoals patiënten die voor de behandeling slechter scoorden op verbale geheugentests in onze studie. Tot slot zal meer kennis over de optimale timing van de interventies, evenals onderzoek naar optimale duur van therapisessies en sessiefrequentie bijdragen aan effectievere behandelingen voor PTSS patiënten in de toekomst.
Dankwoord

Ten eerste wil ik alle deelnemers aan het onderzoek van harte bedanken. Zonder hen was dit onderzoek er niet geweest. Naar het AMC komen voor de nametingen vroeg soms veel van hen. Bedankt voor de tijd en inzet.

Ten tweede wil ik mijn promotores bedanken. Miranda, wat een luxe om als jonge psycholoog na het schrijven van mijn scriptie op jouw afdeling te komen werken. Je hebt me veel vrijheid gegeven om me te ontwikkelen als therapeut en onderzoeker en hebt me nooit beperkt in het doen van veel projecten tegelijkertijd. Waarschijnlijk is dat zo omdat je je zelf ook niet laat beperken in je enthousiasme om alle leuke en interessante dingen die langs komen in te passen. Je bent welverdiend hoogleraar geworden gedurende mijn promotietraject. Bedankt voor je support en voor de snelle feedback op alle stukken die ik je stuurde. Het is prettig samenwerken met jou, en ik vind het leuk dat we die samenwerking de komende tijd kunnen voortzetten in mijn werk als postdoc.

Berthold Gersons, veel dank voor je enthousiasme toen ik in 2004 met de vraag kwam of ik op de BEP-EMDR studie kon promoveren. De kansen die je me hebt gegeven om me te ontwikkelen, ook op het gebied van het geven van cursussen, zijn heel waardevol geweest voor me (en nog steeds!). Door de trainingen heb ik je ook persoonlijk beter leren kennen en veel geleerd van je ‘helikopterview’. Ila en jij zijn inspirerend samen. Ook het beveiligingsproject met de politici, wat gezien zou kunnen worden als een zijspoor in het traject, had ik niet willen missen omdat het me heeft geleerd hoe het pionieren met een onderwerp in zijn werk gaat. Dank je dat je dit aan mij hebt toevertrouwd.

De andere leden van de promotiecommissie, prof. dr. W. van den Brink, prof. dr. M. Sprangers, prof. dr. B. Schmand, prof. dr. M. Grootenhuis en prof. dr. M. van den Hout wil ik bedanken voor het beoordelen van dit proefschrift. Dear prof. dr. U. Schnyder, thank you for being part of the committee. I am honored that you will attend the ceremony.

Mariel, ik heb veel aan jou te danken. Jij begeleidde me bij het schrijven van mijn scriptie, waar uiteindelijk ook een mooi artikel uit is gekomen, en gaf je positieve indruk van mij door aan Miranda. We zijn ongeveer
Summary and Appendix

tegelijkertijd begonnen met het doen van BEP behandelingen en je hebt veel behandelingen in het kader van mijn onderzoek gedaan. Dankjewel dat ik bij jou terecht kon als ik op een moeilijk punt zat met een therapie of in de dataverzameling voor de BEP-EMDR studie. Inmiddels werk je bij GGZ-NHN, maar geven we wel samen cursussen. Ik waardeer het hoe jij tegen dingen aankijkt, je snelle beslissingen, maar ook je warmte als persoon en het feit dat je je collega’s veel gunt. Ik ben heel blij dat je mijn paranimf wil zijn.

Daniël, als broer heb jij voor een ander vakgebied gekozen maar je betrokkenheid bij mijn proefschrift was groot. Je vroeg altijd weer even hoe het ging en hield me scherp als er allemaal andere leuke projecten op me afkwamen, zoals een goede econoom dat doet. Bij reisjes naar het buitenland of andere onderzoeksprojecten vroeg je aan me: “Houd je dan wel genoeg tijd over voor je proefschrift?” Dankjewel dat je naast me wilt staan bij de verdediging.

Theo Hoijtink, jij zag al vanaf het derde jaar van mijn studie psychologie dat de academische wereld mij goed zou ligger en dat ik daar ver in zou komen. Ik had zelf toen vooral het idee dat ik de klinische praktijk in wilde en ook nog niet zo veel vertrouwen in mijn kunnen. Enorm bedankt voor je begrip en de positieve stimulans in de moeilijke periode in mijn leven toen mijn vader net was weggevallen, en daarna. Ik heb met plezier vele jaren een gastcollege gegeven en stagiaires en scribenten begeleid van de afdeling Klinische Psychologie van de VU.

Een onderzoek als dit doe je niet alleen. De collega’s die de dataverzameling en een goede onafhankelijke randomisatie mogelijk maakten, wil ik hierbij van harte bedanken. Noor de Bruijn, Adrienne Freeve, Renee Hutter en Gre Westerveld, wat een mooi onderzoek hebben we met zijn allen neergezet. Ook de secretaresses, Frenny Wiersema en Kitty Schimmel (in herinnering), bedank ik voor hun bijdrage. De stagiaires die metingen deden onder supervisie komt tevens dank toe: Annu Sharma, Mirte de Vries, Anna Wiesenbach, Miriam Spenhoff, en de twee die later collega’s werden: Noor de Bruijn en Rogier Visser. Hartelijk dank aan de studenten die hun M-these schreven op het onderzoek, audio-opnames beluisterden, scoorden en data invoerden: Irene Martens, Chrissy Bakker, Floor van Pelt, Ingrid Stegenga en Melanie Baas. Irene en Melanie bedank ik daarnaast voor hun bijdrage aan de artikelen over hun deel van het onderzoek.

Memory traces of trauma | 191
Speciale dank gaat ook uit naar Ineke Vrijlandt. Ineke, jij speelde een cruciale rol bij de aanmeldingen in de beginjaren van het onderzoek. Daarnaast heb je me veel geleerd over traumatherapie en de optimale betrokkenheid en afstand in het werken met patiënten die traumatische gebeurtenissen hebben meegemaakt. Ik bewonder je kunst en vind het fijn om contact met je te blijven houden.

Alle arts-assistenten die patiënten verwezen en behandelden voor het onderzoek wil ik hierbij ook van harte bedanken. Tevens dank ik alle psychologen die behandelingen uitvoerden voor het onderzoek, in het bijzonder Elianne Schoester.

Joanne Mouthaan, ik vond het heel fijn dat onze onderzoekstrajecten parallel liepen en we daardoor veel konden uitwisselen. Je bent ook een vriendin geworden en het was geweldig om bij congressen een hotelkamer te delen. Op een van de congressen hadden we beide een verschillende vorm van griepp en lagen we uitgeteld op bed als we niet moesten presenteren, maar ook dat mocht de pret niet drukken. Ik kijk uit naar jouw promotie, die er ook gauw aankomt.

Giel-Jan de Vries, bedankt voor alle discussies over geheugen en voor de data-analyses. De discussies maakten de zaken er soms niet gemakkelijker op, maar er is stevig nagedacht over de analyses en het resultaat mag er zeker zijn. Marit Sijbrandij en Ramón Lindauer dank ik ook voor de adviezen en gesprekken over onderzoekszaken. Rosaura Polak, leuk dat wij nog samenwerken met de slaap- en cortisolstudie, ook al ben je nu in opleiding elders.

De huidige Psychotrauma collega’s, Jessie Frijling, Laura Nawijn, Saskia Koch, Mirjam van Zuiden, Christianne van der Meer en Anne Bakker dank ik voor de leuke sfeer op de afdeling. Mirjam ook bedankt voor de kritische kanttekeningen bij de samenvatting.

Marthe van der Pol, dankjewel voor het meeschrijven aan het case report en voor de leuke samenwerking in de eendaagse OCD behandeling. Ron Dekens, hartelijk dank voor het aanmelden van vele patiënten voor het onderzoek en het meeschrijven aan het case report. Ook bedankt voor het uitdoen van het licht in mijn werkkamer ten teken dat het om 19.30 toch echt tijd werd om naar huis te gaan als ik in de aanloop naar een congres aan het overwerken was.

Damiëaan, dank voor de scherpte die je inbracht bij discussies en de coaching bij het schrijven van het case report.
Hans Reitsma, wat ongelofelijk fijn is het om van jou statistisch advies te krijgen. Je legt de zaken zo duidelijk uit dat het uitwerken van de analyses daarna helemaal niet meer zo moeilijk was.

Jan van Amsterdam, dank voor je hulp bij de bepalingen van de stresshormonen en je bijdrage aan het artikel daarover.

Op deze plek wil ik graag ook de collega’s bedanken die weliswaar geen directe rol hadden bij de totstandkoming van het onderzoek en proefschrift, maar die gedurende de eerste anderhalf jaar van de opleiding tot GZ-psycholoog en verdere ontwikkeling als onderzoeker belangrijk zijn geweest. Arnoud van Loon, ik waardeer je humoristische benadering van uitdagingen. Eric Versteeg, dank voor de uitstekende supervisie en je betrokkenheid. Paul Korsten, dank voor de begeleiding; verfrissend om een begeleider op een academische afdeling te treffen bij wie het leren voldoendes te verdragen een leerdoel kan zijn. Dorien Nieman, dank voor de ervaringen die ik mocht opdoen met diagnostiek en behandeling van psychotische stoornissen. De GZ-collega’s Rinske Schepers, Esther Hemelrijk en Mirjam van Tricht (a.k.a. the Fantastic Four), ik heb veel gehad aan de intervisie-lunches met jullie. Kirstin, Rogier en Willeijn, leuk dat jullie nu ook in het traject zitten. En natuurlijk wil ik hier mijn GZ-opleidingsgenoten ook niet vergeten: dank je wel Chawa, Dieke, Ellen, Ilona, Iris, Jasper, Lieke, Lisanne, Marjo-Anne, Marloes, Maud, Lisanne, Patricia en Rosa voor de topsfeer op de opleiding en bij de lunches en borrels!

De collega’s van Centrum ’45, in het bijzonder Ruud Jongedijk, Twan Driessen, Marcella Pomme en Mieke van Harberden wil ik bedanken voor de fijne samenwerking in het kader van de slaapstudie. Lucia Talamini, Winni Hofman en Marieke de Boer, bedankt voor de samenwerking; ik ben geweldig benieuwd naar de resultaten van onze gezamenlijke studie.

Lutz Wittmann, thank you for your friendship and the inspiring times at the trauma conferences. It was great to encourage each other in BEP research and life as a clinician/researcher. I value your perspective on doing research and never forgetting what is important to the patient. I wish you all the best in Berlin.

Bij deze wil ik ook mijn moeder bedanken. Dank je wel dat je me zo hebt gesteund en er voor me bent. Onze band is moeilijk in woorden te vatten. Ik hoop dat papa een glimp kan opvangen van hoe we nu in het leven staan en dat hij trots op ons is.
Christel, wij zijn al heel lang vriendinnen en dat vind ik geweldig. Dank voor je begrip, je luisterend oor en de leuke muzikale uitjes. Antoinet en Wijnie, wat super dat wij vriendinnen zijn geworden tussen de archeologische opgravingen in Griekenland temidden van alle aanwezige juffen, verpleegsters en bouwvakkers! Ik heb genoten van onze gezamenlijke vakanties en citytrips en hoop dat we binnenkort weer een leuk uitje verzinnen. Antoinet, ook heel veel dank voor al je hulp met de layout. Geweldig om te zien dat jij die zo in elkaar draait, terwijl ik dat een vervelende en frustrerende klus vind. Jouw humor is ongeëvenaard. Linda, thank you for the help with the English language check for the main paper of the randomized trial, and for your genuine interest in the whole course of my PhD project. Courtney, I am blessed to have a friend who was willing to make time for a language check of the Introduction and Discussion of this thesis on such short notice. Your help is highly appreciated. Jannie, ik vind het fijn dat wij regelmatig hebben kunnen kletsen over de verschillende fases van promotieonderzoek; we liepen daarin behoorlijk gelijk op. Succes met jouw laatste loodjes! Avantia, bedankt dat je de illustratie voor de cover hebt willen maken. Ik mis je nu je in Curaçao woont, maar gelukkig kom je af en toe naar Nederland. Noemi, dear friend and fellow postdoc researcher in Spain, thank you for the nice and relaxing times during your stays in Amsterdam and the trips to Madrid! I admire your sense of adventure and the spontaneous planning of social life. I hope to visit you again soon. Maybe we will write a book someday about the road to getting your PhD; we will have plenty of subjects and stories!

Lieve Arjen, ik ben zo blij dat ik je heb leren kennen en met je getrouwd ben. Jij past zo goed bij mij. Je helpt me om dingen te relativeren en hebt me enorm gesteund in de afgelopen drukke periode. Het leven is mooi met jou en ik ben heel benieuwd naar alle avonturen die we in de toekomst gaan beleven. You are my sunshine.


---

Memory traces of trauma

194
Curriculum Vitae

Mirjam J. Nijdam was born in Amsterdam, The Netherlands, on June 8th, 1980. In 1998, she completed her pre-university education (VWO) at the Pascal College in Zaandam and started her studies in Psychology at the Free University in Amsterdam. In 2003, she obtained her Master’s degree in Clinical Psychology with honors. Her master’s thesis was written at the Center for Psychological Trauma at the Department of Psychiatry of the Academic Medical Center at the University of Amsterdam, and was later adapted to one of the chapters of the current thesis.

Since 2003, Mirjam has been employed as a psychologist and researcher at the Department of Psychiatry at the Academic Medical Center, combining her passion for patient care and research. From 2004-2011, she conducted a parttime PhD project on a randomized controlled trial comparing Eye Movement Desensitization and Reprocessing (EMDR) therapy and Brief Eclectic Psychotherapy in the treatment of posttraumatic stress disorder, of which the results are described in the present thesis. From 2006 to 2008 she has conducted a study on the psychosocial effects of terrorist threats and close protection on Dutch politicians, commissioned by the National Coordinator for Security and Counterterrorism. She is a trainer and supervisor in Brief Eclectic Psychotherapy for PTSD since 2008.

From 2012, she started her clinical training as a healthcare psychologist (GZ postdoctoral education) to obtain her clinical registration and worked at the Departments for Early Psychosis and Mood Disorders. She currently also holds a postdoc position investigating the association between sleep and memory for emotional and neutral information in police officers and veterans with posttraumatic stress disorder, in collaboration with the Brain and Cognition Group at the University of Amsterdam and Arq Psychotrauma Expert Group. In 2013, she received the Francine Shapiro Award of the EMDR Europe Association for her work.

Centrum (AMC) aan de Universiteit van Amsterdam. De scriptie werd later herschreven en als hoofdstuk opgenomen in het huidige proefschrift.


Vanaf 2012 is ze begonnen met haar opleiding tot gezondheidszorgpsycholoog om haar klinische registratie te behalen en werkte ze achtereenvolgens op de zorglijnen Vroege Psychose en Stemmingsstoornissen. Ze heeft daarnaast een postdoc aanstelling waarbij ze onderzoek doet naar de samenhang tussen slaap en het geheugen voor emotionele en neutrale informatie bij politieagenten en veteranen met een posttraumatische stress stoornis, in samenwerking met de Brain and Cognition groep aan de Universiteit van Amsterdam en Arq Psychotrauma Expert Groep. In 2013 ontving ze de Francine Shapiro Award van de Europese EMDR vereniging voor haar werk.
List of publications

Papers


Submitted papers


Book chapters


Reports


Summary and Appendix

Psychological Trauma, Academic Medical Center at the University of Amsterdam.


Memory traces of trauma

199
## Portfolio

**Name PhD student:** M.J. Nijdam  
**PhD period:** September 2004-December 2011  
**Name PhD supervisor:** Prof. dr. M. Olff, Prof.dr. B.P.R. Gersons

### 1. PhD training

<table>
<thead>
<tr>
<th>General courses</th>
<th>Year</th>
<th>Workload (ECTS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- The AMC World of Science</td>
<td>2004</td>
<td>0.7</td>
</tr>
<tr>
<td>- Practical Biostatistics</td>
<td>2006</td>
<td>1.1</td>
</tr>
<tr>
<td>- Better use of PubMed and other medical databases</td>
<td>2006</td>
<td>0.1</td>
</tr>
<tr>
<td>- BROK (‘Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers’)</td>
<td>2013</td>
<td>0.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specific courses</th>
<th>Year</th>
<th>Workload (ECTS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Training Brief Eclectic Psychotherapy</td>
<td>2004</td>
<td>0.9</td>
</tr>
<tr>
<td>- EMDR Level 1 training</td>
<td>2004</td>
<td>0.9</td>
</tr>
<tr>
<td>- EMDR Level 2 training</td>
<td>2005</td>
<td>0.9</td>
</tr>
<tr>
<td>- Training Well-being therapy</td>
<td>2006</td>
<td>0.7</td>
</tr>
<tr>
<td>- Training Trauma-focused CBT</td>
<td>2009</td>
<td>0.4</td>
</tr>
<tr>
<td>- Training Imaginary Rescripting and Reprocessing Therapy</td>
<td>2011</td>
<td>0.4</td>
</tr>
<tr>
<td>- Training in administration of SI-PTSD</td>
<td>2004</td>
<td>0.2</td>
</tr>
<tr>
<td>- Training in administration of SCID-I/P</td>
<td>2006</td>
<td>0.4</td>
</tr>
<tr>
<td>- Training in administration of MINI-Plus</td>
<td>2009</td>
<td>0.2</td>
</tr>
<tr>
<td>- Training in administration of CAPS</td>
<td>2009</td>
<td>0.2</td>
</tr>
</tbody>
</table>
### Seminars, workshops and master classes

<table>
<thead>
<tr>
<th>Event</th>
<th>Years</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly department seminars</td>
<td>2004-2011</td>
<td>8</td>
</tr>
<tr>
<td>Trauma and neurobiology workgroup seminars</td>
<td>2005-2011</td>
<td>1</td>
</tr>
<tr>
<td>European Workshops on Traumatic Stress</td>
<td>2005</td>
<td>0.7</td>
</tr>
<tr>
<td>Symposium Goed Gestemd III</td>
<td>2005</td>
<td>0.2</td>
</tr>
<tr>
<td>Cognition and the Sleeping Brain</td>
<td>2005</td>
<td>0.2</td>
</tr>
<tr>
<td>Symposium Blijvend Goed Gestemd</td>
<td>2006</td>
<td>0.2</td>
</tr>
<tr>
<td>Masterclass by prof. A. Shalev</td>
<td>2008</td>
<td>0.2</td>
</tr>
<tr>
<td>Masterclass by dr. M. Friedman</td>
<td>2009</td>
<td>0.2</td>
</tr>
<tr>
<td>Masterclass by prof. M. Cloitre</td>
<td>2010</td>
<td>0.4</td>
</tr>
<tr>
<td>Masterclass by prof. L. Nadel</td>
<td>2011</td>
<td>0.2</td>
</tr>
</tbody>
</table>

### Presentations

<table>
<thead>
<tr>
<th>Event</th>
<th>Years</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plenary contribution to the Heijermans lecture; continuing education for occupational doctors.</td>
<td>2006</td>
<td>0.5</td>
</tr>
<tr>
<td>Plenary lecture for conference on Psychotrauma and work for occupational and insurance doctors.</td>
<td>2007</td>
<td>0.5</td>
</tr>
</tbody>
</table>

### (Inter)national conferences

<table>
<thead>
<tr>
<th>Event</th>
<th>Years</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two poster presentations at the annual meeting of the International Society for Traumatic Stress Studies.</td>
<td>2005, 2006</td>
<td>1</td>
</tr>
<tr>
<td>Five oral presentations at the annual meeting of the International Society for Traumatic Stress Studies</td>
<td>2007-2011</td>
<td>2.5</td>
</tr>
<tr>
<td>Oral presentation at the European EMDR Conference.</td>
<td>2009</td>
<td>0.5</td>
</tr>
<tr>
<td>Two oral presentations at the European Conference on Traumatic Stress.</td>
<td>2009, 2011</td>
<td>1</td>
</tr>
<tr>
<td>Oral presentation at the World Congress of Psychotherapy.</td>
<td>2010</td>
<td>0.5</td>
</tr>
<tr>
<td>Poster presentation at the European College of Neuropsychopharmacology Congress.</td>
<td>2010</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Summary and Appendix

2. Teaching

<table>
<thead>
<tr>
<th>Lecturing</th>
<th>Year</th>
<th>Workload (ECTS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 courses of Research skills seminar, Dept of Medicine</td>
<td>2004-2005</td>
<td>2</td>
</tr>
<tr>
<td>10 lectures on PTSD, EMDR, CBT for anxiety disorders for Medicine students and Psychology students</td>
<td>2004-2011</td>
<td>2</td>
</tr>
<tr>
<td>9 days of BEP training</td>
<td>2008-2010</td>
<td>2</td>
</tr>
<tr>
<td>3 BEP workshops</td>
<td>2008-2010</td>
<td>0.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Supervising</th>
<th>Year</th>
<th>Workload</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supervising 6 MSc students during clinical internships (6 months)</td>
<td>2004-2009</td>
<td>12</td>
</tr>
<tr>
<td>Supervising 5 MSc students writing their Master’s thesis (3 months)</td>
<td>2007-2010</td>
<td>5</td>
</tr>
<tr>
<td>Supervising therapists in BEP</td>
<td>2010-2011</td>
<td>1</td>
</tr>
</tbody>
</table>

3. Parameters of Esteem

<table>
<thead>
<tr>
<th>Awards and Prizes</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Francine Shapiro Award, EMDR Europe Association</td>
<td>2013</td>
</tr>
</tbody>
</table>