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