Memory traces of trauma: Neurocognitive aspects of and therapeutic approaches for posttraumatic stress disorder
Nijdam, M.J.

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

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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,
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, & Bremner, 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
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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.
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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
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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...
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.
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 α=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).
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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></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>
</tbody>
</table>

Clinical features
Co-morbid axis I disorders (SCID-I, Patient Edition)

| Major depressive disorder | 25 | 61.0 | 22 | 46.8 | 1.77 | 1 | 0.18 |
| Anxiety disorder other than PTSD | 10 | 24.4 | 6 | 12.8 | 1.99 | 1 | 0.16 |

On psychoactive medication

| On SRRI | 9 | 22.0 | 8 | 17.0 | 0.34 | 1 | 0.56 |
|         | mean | S.D. | mean | S.D. | t | df | p    |

| Age | 39.0 | 10.78 | 41.6 | 11.3 | 1.11 | 86 | 0.27 |
| PTSD Total score (SI-PTSD) | 39.2 | 6.9 | 38.3 | 5.9 | 0.68 | 86 | 0.50 |
| PTSD Total score (IES-R) | 81.3 | 14.1 | 69.9 | 21.3 | 2.99 | 86 | <0.01 |
| HADS Depression | 11.7 | 3.9 | 11.0 | 4.1 | 0.81 | 86 | 0.42 |
| HADS Anxiety | 13.5 | 4.2 | 12.2 | 3.6 | 1.47 | 86 | 0.15 |

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.
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 )^a)</th>
<th>Eye Movement Desensitisation and Reprocessing (( n=47 )^a)</th>
<th>Time effect</th>
<th>Time x treatment condition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-treatment mean±S.D.</td>
<td>Post-treatment mean±S.D.</td>
<td>Pre-treatment mean±S.D.</td>
<td>Post-treatment 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±11.4</td>
<td>50.4±11.9</td>
<td>50.9±11.7</td>
<td>55.8±9.3</td>
</tr>
<tr>
<td>Trials 1-5</td>
<td>10.5±11.7</td>
<td>10.4±11.7</td>
<td>11.4±12.3</td>
<td>12.3±12.8</td>
</tr>
<tr>
<td>ST Free Recall</td>
<td>3.0±3.0</td>
<td>3.1±3.0</td>
<td>3.2±2.7</td>
<td>3.2±2.6</td>
</tr>
<tr>
<td>ST Cued Recall</td>
<td>11.9±2.6</td>
<td>12.0±3.0</td>
<td>12.2±2.7</td>
<td>13.2±2.6</td>
</tr>
<tr>
<td>LT Free Recall</td>
<td>11.2±3.3</td>
<td>12.0±3.7</td>
<td>11.7±3.5</td>
<td>13.0±3.0</td>
</tr>
<tr>
<td>LT Cued Recall</td>
<td>3.3±3.2</td>
<td>3.7±3.5</td>
<td>3.5±3.0</td>
<td>3.0±2.7</td>
</tr>
<tr>
<td>LT Recognition</td>
<td>4.0±2.8</td>
<td>4.0±2.8</td>
<td>4.1±2.7</td>
<td>4.2±2.7</td>
</tr>
<tr>
<td>RBMT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate Recall</td>
<td>16.7±5.8</td>
<td>21.4±7.1</td>
<td>17.1±6.4</td>
<td>21.4±7.1</td>
</tr>
<tr>
<td>Delayed Recall</td>
<td>12.7±5.6</td>
<td>17.3±6.4</td>
<td>13.8±6.2</td>
<td>17.6±7.6</td>
</tr>
<tr>
<td>TMT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part A</td>
<td>35.7±13.7</td>
<td>32.0±6.2</td>
<td>34.4±14.4</td>
<td>27.9±19.9</td>
</tr>
<tr>
<td>Part B</td>
<td>88.6±35.4</td>
<td>75.6±37.5</td>
<td>80.3±37.5</td>
<td>70.4±37.5</td>
</tr>
<tr>
<td>Stroop</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Card 2</td>
<td>67.1±20.7</td>
<td>64.6±21.8</td>
<td>63.3±14.0</td>
<td>60.0±13.1</td>
</tr>
<tr>
<td>Card 3</td>
<td>111.7±45.4</td>
<td>102.6±46.7</td>
<td>104.4±46.7</td>
<td>94.8±46.6</td>
</tr>
<tr>
<td>Interference</td>
<td>44.8±32.1</td>
<td>42.1±34.1</td>
<td>35.2±34.1</td>
<td>5.44</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 \( d \).

\(^a\) Sample size varies slightly across observations because of missing data on a specific measure or outliers (total \( n = 83-88 \)).
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Associations between 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>CVLT</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>RBMT</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>TMT</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>Stroop</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 \( n=83-88 \)).

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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 $p>0.05$).
Chapter 6

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

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, Lazorve, & van der Kolk, 1999; Lansing, Amen, Hanks, & Rudy, 2005; Oh & Choi, 2007; Lindauer et al., Memory traces of trauma
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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, Fagiolini, & 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
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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


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