Memory traces of trauma: Neurocognitive aspects of and therapeutic approaches for posttraumatic stress disorder
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Chapter 7

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

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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 not subside. 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 

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

Both Rivermead immediate recall and delayed recall indices were found to be significantly associated with all CVLT indices (all \( r \geq .29, all \ p \leq .001 \)). 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 (β=-8.1; 95%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 β:-7.4 vs. -5.3). However the results on the Rivermead memory measures showed opposite effects (immediate retrieval: β=-5.6; delayed retrieval: β=-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.
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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.
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Figure 1. Receiver operating characteristic (ROC) curve for CVLT long term cued memory performance at 6 weeks and 17 weeks after treatment.

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.
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, & Bremer, 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.

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multidimensional meta-analysis of psychotherapy for PTSD.


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