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Response to Psychotherapy for Posttraumatic Stress Disorder: The Role of Pretreatment Verbal Memory Performance

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ABSTRACT

Objective: Neuropsychological studies have consistently demonstrated impaired verbal memory in posttraumatic stress disorder (PTSD). Trauma-focused treatment for PTSD is thought to rely on memory, but it is largely unknown whether treatment outcome is influenced by memory performance. The aim of the study, therefore, was to examine the relationship between verbal memory performance and treatment response to trauma-focused psychotherapy.

Method: Participants were referred to our outpatient clinic and recruited between December 2003 and January 2009 upon diagnosis of PTSD according to *DSM-IV*. Secondary analyses of a randomized controlled trial comparing eye movement desensitization and reprocessing therapy (n = 70) and brief eclectic psychotherapy (n = 70), a cognitive-behavioral intervention, are reported. Response to treatment was measured by self-reported PTSD symptom severity (Impact of Event Scale—Revised) over 17 weeks. Pretreatment verbal memory measures (California Verbal Learning Test, Rivermead Behavioral Memory Test) were included in the mixed linear model analyses in order to investigate the influence of memory on treatment outcome.

Results: Pretreatment encoding, short-term retrieval, long-term retrieval, and recognition performance were significantly associated with treatment response in terms of self-reported PTSD symptom severity for both treatments ($P \leq .013$). Receiver operating characteristic curves predicting treatment response with pretreatment memory indices showed that 75.6% of the patients could be correctly classified as responder.

Conclusions: Poor verbal memory performance represents a risk factor for worse treatment response to trauma-focused psychotherapy. Memory measures can be helpful in determining which patients are unable to benefit from trauma-focused psychotherapy. Future research should explore how treatment perspectives of patients with poor verbal memory can be improved.

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Symptoms such as reexperiencing a traumatic event in one's mind, avoidance of thoughts about the trauma, and concentration problems characterize posttraumatic stress disorder (PTSD). PTSD may be perceived as a disorder of memory,[1] as scenes from the terrifying events from the past are remembered far too well, and everyday tasks that do not involve danger are subject to forgetfulness and decreased attention. Research has indeed confirmed that PTSD is associated with mild to moderate neuropsychological deficits on emotionally neutral tasks, most consistently in verbal memory and sustained attention.[2–4] Poor verbal memory performance has proven to be related to PTSD even when studies have controlled for comorbidity,[5] attentional difficulties, and intelligence.[6] Prospective studies have also shown that pretrauma impairments in verbal memory are a risk factor for developing PTSD symptoms later on.[7]

According to several neurocognitive studies, there is an inverse association between neuropsychological functioning and reexperiencing symptoms such as flashbacks and nightmares. The more reexperiencing symptoms PTSD patients had, the worse their capacity to inhibit irrelevant information on emotionally neutral tasks[8] and the worse their performance on verbal memory tasks.[7,9] 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. This may also be true for the benefit patients draw from trauma-focused psychotherapy, as not all patients benefit equally from these interventions.[10] Therapeutic elements applied in trauma-focused interventions are a form of imaginal exposure and cognitive restructuring,[11] and these processes are assumed to be dependent on how well a person can store and retrieve new information.

It is still largely unknown if the extent to which the memory system is deregulated hinders PTSD patients' ability to benefit from treatment. So far, only a single study[12] has provided evidence that verbal memory predicts treatment outcome in PTSD patients who underwent trauma-focused cognitive-behavioral therapy (TF-CBT). Because of its limited sample size and its application of one type of psychological intervention, it is necessary to replicate and extend the study's finding. The aim of the current study, therefore, is to examine the relationship between verbal memory performance and treatment outcome in a larger sample and to different types of trauma-focused psychotherapy: eye movement desensitization and reprocessing (EMDR) and brief eclectic psychotherapy (BEP), a form of TF-CBT. We hypothesized that pretreatment poorer verbal memory performance for emotionally neutral information would be associated with worse treatment outcome in both treatment conditions.

METHOD

Participants and Procedure

Participants were treatment-seeking outpatients who were referred to the Center for Psychological Trauma at the Department of

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- Patients who have posttraumatic stress disorder (PTSD) have difficulties remembering verbal information, which may interfere with treatment.
- Patients with PTSD who poorly remember verbal information in the short and long term appeared to have a less favorable treatment response when they received trauma-focused psychotherapy.

Psychiatry at the Academic Medical Center of the University of Amsterdam between December 2003 and January 2009. If a PTSD diagnosis was presumed at intake, the patients were approached for participation in the study. 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, and (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*, and (4) severe personality disorder according to the Structured Clinical Interview for *DSM-IV-TR* Axis II Personality Disorders screener[13] and *DSM-IV* criteria for personality disorder. A total of 42 patients were excluded because of severe comorbid conditions. 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 these conditions. If patients were on pharmacologic treatment, a stable regimen for at least 1 month was required before entering the study. After complete description of the study to the subjects, written informed consent was obtained.

A total of 140 patients were randomized to receive either EMDR (n = 70)[14] or BEP (n = 70).[15] Brief eclectic psychotherapy is a manualized treatment that mainly consists of trauma-focused cognitive-behavioral elements such as psychoeducation, imaginal exposure to the traumatic event, writing assignments, and cognitive restructuring. Some elements can also be understood from other therapeutic approaches, such as objects that remind the person of the trauma, performance of a farewell ritual, and meaning making in response to the trauma. Eye movement desensitization and reprocessing is a manualized intervention in which the most distressing images of the traumatic event are identified and processed by making eye movements in alternation with the patient's own associations. Both treatments were administered as in clinical practice, allowing for the number of sessions to vary depending on recovery. Treatment completers received a mean of 6.5 (SD = 3.8) EMDR sessions of 90 minutes or a mean of 14.7 (SD = 4.5) BEP sessions of 45 minutes. Treatment duration did not significantly differ between the treatment conditions ($P = .77$). Diagnostic assessments were performed by independent, trained assessors preintervention (T0), after the exposure phase (T1 = 6 weeks on average) and after both interventions were finished (T2 = 17 weeks). Self-reported PTSD symptom severity was assessed at every weekly session. Memory measures were administered at T0. The study protocol was approved by the Institutional Medical Ethics Committee of the Academic Medical Center. The trial was registered at ISRCTN.com (identifier: ISRCTN64872147). Further details of the study design are described elsewhere.[16]

Memory Performance Measures

Verbal memory was measured using the California Verbal Learning Test (CVLT)[17] and the Rivermead Behavioural Memory Test (RBMT).[18] The CVLT was designed to measure encoding, short-term retrieval, long-term retrieval, and recognition of words. A 16-item grocery list is presented 5 times (list A), and patients recall as many items as possible after each presentation. The sum of the correct responses on these 5 trials is a measure of encoding performance (range, 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 for list A is measured on a 44-item list including items of list A, B, and unfamiliar words (range, 0–44). Psychometric properties of the CVLT are sufficient.[19]

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 2 newspaper excerpts read out loud to the patient. The patient recalls the excerpt 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 2 paragraphs, as defined by the manual, determines the test score (range, 0–42). The RBMT has shown to be a valid and reliable indicator of memory impairment.[20]

Treatment Outcome Measures

Response to trauma-focused psychotherapy was determined based on the Impact of Event Scale—Revised (IES-R),[21] administered every week, and the Structured Interview for PTSD (SI-PTSD),[22] administered at T0, T1, and T2.

The IES-R is a 22-item self-report questionnaire that measures the severity of PTSD symptoms in the last 7 days. Unlike the original revised version in which categories from 0 to 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.[23]

The SI-PTSD is a structured interview that operationalizes the *DSM-IV* criteria for PTSD, consisting of 17 items each scored on a 5-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.[22,24]

Table 1. Baseline Demographic, Clinical, and Neuropsychological Characteristics of the Sample (n = 140)

Characteristic	n	%
Female sex	79	56.4
Education		
Low	31	22.1
Middle	67	47.9
High	42	30.0
Marital status		
Single	69	49.3
Married/living together	61	43.6
Divorced	9	6.4
Widow	1	0.7
Trauma		
Assault	74	52.9
Accident	26	18.6
Sexual assault	16	11.4
War-related	7	5.0
Other	7	5.0
Comorbid Axis I disorders (SCID-I)		
Major depressive disorder	84	60.0
Anxiety disorder other than PTSD	22	15.7
	Mean	SD
Age, y	37.8	11.4
SI-PTSD total score	39.8	6.2
IES-R PTSD total score	76.4	19.1
CVLT		
Encoding	49.4	10.6
Retrieval, short-term	10.9	3.0
Retrieval, long-term	11.3	3.1
Cued retrieval, short-term	11.9	2.7
Cued retrieval, long-term	12.0	2.8
Recognition, long-term	41.4	3.1
RBMT		
Retrieval, short-term	16.0	6.1
Retrieval, long-term	12.3	5.9

Abbreviations: CVLT = California Verbal Learning Test, IES-R = Impact of Event Scale—Revised, PTSD = posttraumatic stress disorder, RBMT = Rivermead Behavioral Memory Test, SCID-I = Structured Clinical Interview for *DSM-IV* Axis I disorders, SI-PTSD = Structured Interview for PTSD.

Clinical characteristics that could potentially influence memory performance were assessed at pretreatment and controlled for in the analyses. A comorbid depression diagnosis was determined using the Structured Clinical Interview for *DSM-IV* Disorders,[25] a widely used interview with high reliability and validity.[26]

Data Analysis

χ^2 Tests and independent *t* tests were used to compare demographic and clinical characteristics between the treatment groups. Repeated-measures analyses were used to study changes over time between the treatment groups. Mixed linear models were used to take into account that measurements within the same individual are correlated and to allow the models to calculate estimates when data were missing at certain assessments. An autoregressive pattern was imposed on the covariance structure for measurements within the same individual (AR1). The IES-R scores at the 17 postmeasurements were modeled as a function of the intervention given (BEP, EMDR), time since intervention (factor with 17 levels), pretreatment IES-R score (continuous), pretreatment memory performance measure (*Z*-transformed, continuous), pretreatment diagnosis of MDD (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. *P* values ≤ .05 were considered statistically significant, and 2-tailed tests were used throughout. Post hoc receiver operating characteristic (ROC) curves were fitted with remission from the PTSD diagnosis, as determined by SI-PTSD, as reference.

RESULTS

Pretreatment demographic, clinical, and neuropsychological characteristics are shown in Table 1. No differences were found between the treatment conditions, except that the IES-R total score was significantly higher in the BEP group than in the EMDR group ($t = 2.25$, $P = .03$), for which we corrected in our analyses. Significant correlations were found between pretreatment PTSD symptom severity and CVLT sum of trials 1–5, CVLT long-term retrieval, CVLT long-term cued retrieval, RBMT short-term retrieval, and RBMT long-term retrieval (all *P* values ≤ .028).

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 PTSD scores on the IES-R. The mixed-model analyses demonstrated significant interaction effects of time with treatment condition (all *P* values < .001). Even though the mixed-model analysis adjusted for the influence of memory performance on PTSD scores, these effects were consistent with results previously reported for this RCT.[16] All individual memory measures influenced treatment outcome significantly (all *P* values ≤ .013). Because the memory measures were all *Z*-transformed, the relative strength of effect of the individual measures could be reciprocally compared. The CVLT long-term cued retrieval demonstrated the largest strength of effect (β = −8.1; 95% CI, −12.7 to −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 PTSD scores on the IES-R scale. The 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 RBMT memory measures showed opposite effects (short-term retrieval: β = −5.6; 95% CI, −10.0 to −1.3; long-term retrieval: β = −3.7; 95% CI, −8.2 to 0.7). No effect of memory performance on treatment condition was found (all *P* values ≥ .323).

Pretreatment measurement of IES-R significantly affected PTSD scores at the 17 postmeasurements (all *P* values < .001). Major depressive disorder at pretreatment was included in the analysis to control for the alternative interpretation that the influence of memory on PTSD scores is 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 retrieval, CVLT long-term

Table 2. Intent-To-Treat Analyses of the Effects of Memory and Treatment on Changes in Posttraumatic Stress Disorder (PTSD) Scores on the Impact of Event Scale—Revised (n = 127)

Memory	Memory				Time		Condition		Time × Condition		Memory × Condition	
Measure (*Z*-transformed)	β	95% CI	*F*	*P*	*F*	*P*	*F*	*P*	*F*	*P*	*F*	*P*
CVLT												
Encoding	−5.2	−9.6 to −0.8	17,565	< .001	18,785	< .001	10,895	.001	3,985	< .001	0.981	.323
Retrieval, short-term	−4.2	−8.7 to 0.3	8,922	.003	18,402	< .001	8,769	.004	3,984	< .001	0.197	.657
Retrieval, long-term	−6.8	−11.0 to −2.6	23,703	< .001	18,938	< .001	10,340	.002	4,014	< .001	0.257	.613
Cued retrieval, short-term	−6.5	−11.0 to −2.0	18,812	< .001	18,856	< .001	10,608	.001	4,007	< .001	0.118	.731
Cued retrieval, long-term	−8.1	−12.7 to −3.4	21,808	< .001	18,871	< .001	8,579	.004	4,006	< .001	0.245	.621
Recognition, long-term	−7.2	−12.7 to −1.8	13,238	< .001	18,708	< .001	8,875	.003	4,004	< .001	0.476	.491
RBMT												
Retrieval, short-term	−5.6	−10.0 to −1.3	15,688	< .001	18,228	< .001	11,195	.001	3,969	< .001	0.254	.615
Retrieval, long-term	−3.7	−8.2 to 0.7	6,273	.013	18,068	< .001	10,627	.001	3,975	< .001	0.113	.737

Abbreviations: CVLT = California Verbal Learning Test, RBMT = Rivermead Behavioral Memory Test.

recognition, and RBMT short- and long-term retrieval incorporated in the analyses (all *P* values ≤ .046).

Similar significant associations were found between all individual memory measures and changes in the separate PTSD symptom clusters reexperiencing, avoidance, and hyperarousal (all *P* values ≤ .035, except for the association between CVLT short-term retrieval and avoidance, which was found to be significant at trend level ($P = .056$).

Simultaneous Testing of the Influence of Memory Measures on Treatment Outcome

Because all individual memory measures 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, 2 separate mixed model analyses were performed in which we added either all the CVLT or all the RBMT measures to the model, while removing the interaction term between memory measure and treatment condition from the analyses. When all CVLT measures were incorporated into the model, we found that only CVLT short-term retrieval significantly influenced PTSD values ($F_{1,145} = 5.389$, $P = .022$). When RBMT measures were incorporated into the model, the effect of short-term retrieval was found to be statistically significant ($F_{1,145} = 12.195$, $P = .001$). Thus, both CVLT and RBMT analyses demonstrated the effects of short-term memory performance on change in PTSD scores.

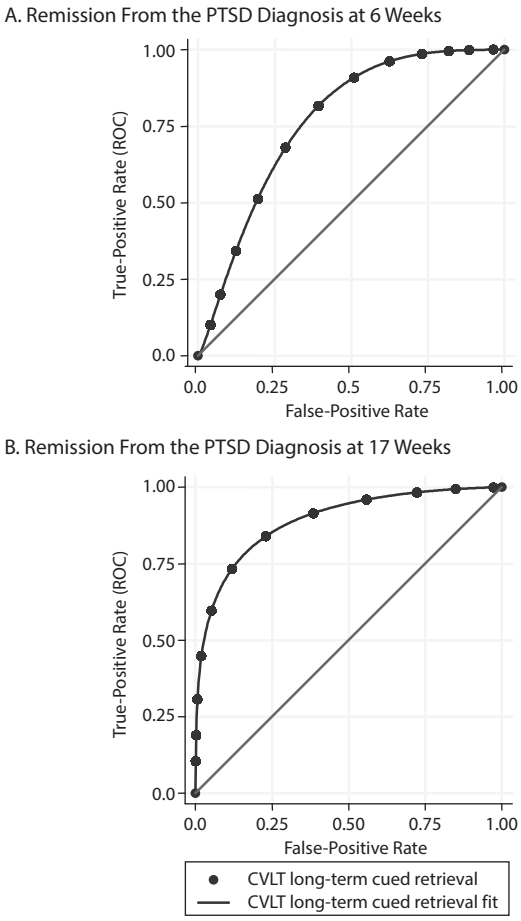
Can Pretreatment Memory Performance Reliably Predict Treatment Outcome?

The above findings raised the question whether pretreatment memory performance could reliably predict treatment success in PTSD patients with adequate sensitivity and specificity. To answer this question, we fitted ROC curves post hoc for each memory measure with patient status of having remitted from the diagnosis of PTSD (defined as no longer fulfilling the criteria of the PTSD diagnosis according to SI-PTSD) as reference after 6 weeks of treatment (70 remitted out of 95 observations) and at the end of treatment (81 remitted out of 90 observations) irrespective of treatment condition. Due to attrition, totals do not reach the number of 140 as included in previous statistical analyses. For remission from the PTSD diagnosis at 6 weeks after start of treatment, areas under the curve (AUCs) for all memory measures ranged between 0.62 and 0.75. For remission of PTSD at the end of treatment, memory measures demonstrated AUCs ranging from 0.76 to 0.91. The CVLT long-term cued retrieval gave the highest AUCs for both time points (Figure 1). However, AUCs of most memory measures did not significantly differ from CVLT long-term cued retrieval, except for CVLT long-term recognition ($\chi_1 = 4.802$, $P = .028$) and CVLT short-term cued retrieval ($\chi_1 = 4.115$, $P = .043$), but only at 6 weeks after treatment. A cutoff point of 11 or higher of CVLT long-term cued retrieval 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.

DISCUSSION

This study investigated the effect of verbal memory performance for emotionally neutral information in PTSD patients on their response to 2 types of 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 degree of change in self-reported PTSD symptoms. The effects of memory performance on PTSD scores were found to be strongest for long-term retrieval, were found for encoding and retrieval of both separate words and of a meaningful narrative, and were found to be independent of treatment condition. The effects for verbal memory performance were robust, since they were found to be independent of pretreatment severity of PTSD symptoms and major depression. Moreover, pretreatment memory indices were found to predict response to treatment as defined by no longer fulfilling the criteria of the PTSD diagnosis with good levels of sensitivity and specificity. These findings extend results of a small study[12] that demonstrated the association between verbal memory and treatment response for TF-CBT in PTSD patients 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 California Verbal Learning Test (CVLT) Long-Term Cued Memory Performance at 6 Weeks (n = 95) and 17 Weeks (n = 90) After Treatment



Abbreviation: PTSD = posttraumatic stress disorder.

The present study suggests that the degree to which the memory system is functioning, or rather is dysfunctioning, predicts whether PTSD patients can benefit from trauma-focused psychotherapy. According to psychological theories of PTSD,[11,27] in trauma-focused psychotherapy the patient deliberately focuses on the content of the intrusions by imaginal exposure and cognitive restructuring. In this process, traumatic memories are reconsolidated and assigned a spatial and temporal context. This enables the person to place the traumatic experiences and the sense of threat in the past, leading to a reduction in reexperiencing symptoms. Our study suggests that this therapeutic process is more restricted when PTSD patients have a more attenuated verbal memory performance before treatment. As a result, 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.[28] Interestingly, both smaller rostral anterior cingulate volumes and pretreatment hyperresponsivity of the amygdala and ventral anterior cingulate during fear processing have been found to predict poor treatment response in TF-CBT.[29,30] Different areas of the fear network may thus 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 2 forms of standardized trauma-focused psychotherapy. A limitation of this study was that we were not able to administer postassessments to a substantial number of patients after their treatment, but we were able to calculate estimates for missing data points in the linear mixed models. A further limitation was that we could not control for intelligence and attention because no separate measures in those domains were administered. It is possible, but unlikely, that overall intelligence and attention account for the findings of the current study, as these were not associated with treatment response in a previous study.[12]

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. Although memory for information embedded in a meaningful narrative seems most relevant for making progress in trauma-focused psychotherapy, memory for separate words appeared to be equally strongly related to treatment response in our study. A clinical implication of our findings is that memory measures may indicate who will probably benefit from treatment and who is unlikely to benefit. Advantages of verbal memory instruments are that they are noninvasive, 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. Patients with PTSD 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 in most PTSD treatment guidelines. If it is presumed that these memory problems are acquired by PTSD or coexisting disorders, it may be useful to offer this patient group selective serotonin reuptake inhibitors first, as there is some evidence that these medications improve verbal memory.[31] This may improve these patients' ability to benefit from trauma-focused psychotherapy. Other possibilities are elementary adaptations to trauma-focused psychotherapy, which may be useful independent of whether the verbal memory problems are acquired or preexisting. Examples include 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 in order to reduce demands on verbal memory.[11]

Future research could further explore other potentially relevant factors for response to trauma-focused

psychotherapy, such as autobiographical memory, selective and sustained attention, and repeated exposure to threat stimuli.[32] Selective attention has also proven to be related to PTSD after controls for mediators were added.[33] Visual memory is generally less impaired in PTSD than verbal memory[3]; therefore, visual enhancers to the therapy could be beneficial. An attempt in this direction is virtual reality enhancement of imaginal exposure,[34] 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,[2,3] real-world situations involve more complex processing than a test situation in which distraction is minimal.[35] 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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