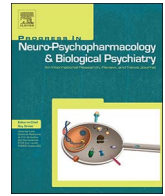




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Deficits in episodic memory and mental time travel in patients with post-traumatic stress disorder



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ABSTRACT

Post-traumatic stress disorder (PTSD) is characterized by impairments in mnemonic functions, especially in the domain of episodic memory. These alterations might affect different aspects of episodic memory functioning. Here we tested PTSD patients and healthy controls (matched for age, sex and education) in a newly developed virtual reality episodic memory test (VR-EMT), a test for mental time travel, episodic future thinking, and prospective memory (M3xT). In a cross-validation experiment, their performance was further evaluated in the Rivermead Behavioral Memory Test (RBMT). PTSD patients demonstrated impairments in episodic memory formation and mental time travel and showed difficulties in utilizing information from episodic memory to solve problems. Diminished attention and concentration in PTSD did not account for performance deficits in these tasks but higher levels of negative arousal were found in PTSD patients. Furthermore, performance in the VR-EMT and RBMT in PTSD patients correlated negatively with self-reported measures of stress and depression. Our results suggest that deficits in episodic memory formation and mental time travel in PTSD lead to difficulties in utilizing the content of episodic memories for solving problems in the present or to plan future behavior. Clinical implications of these findings and suggestions for cognitive-behavioral treatment of PTSD are discussed.

1. Introduction

The episodic memory system allows us to encode specific autobiographical information of events that we have experienced in terms of “what happened,” “where it happened,” and “when it happened” (Dere et al., 2010; Pause et al., 2013; Zlomuzica et al., 2014). Episodic memories also contain perceptions, thoughts, emotions, and feelings we had during that experience. The concept of episodic memory has emerged as a central framework for examining the psychological and neurobiological processes that contribute to the development of PTSD. Current psychological treatment approaches of PTSD such as the (narrative) exposure therapy have revolved around the phenomena related to episodic memory in PTSD (Ehlers and Clark, 2000). Thus, a better understanding of aberrant episodic memory dysfunctions in the context of PTSD is important for both, the etiology and therapeutic management of this highly devastating disorder.

The idea that intrusions and flashbacks that are associated with PTSD might be a consequence of an undamped activation of a pathological episodic memory for the trauma experience has received considerable empirical support (Brewin, 2014; Isaac et al., 2006; Moradi et al., 2008). Similar to other emotionally relevant episodic memories, trauma-related memories are highly vivid and can be activated by either trauma-related stimuli or “spontaneously” due to retrieval-cue generalization leading to the patient's experience of re-living the traumatic episode (Brewin, 2015; Tulving, 2001, 2002).

Although there is ample literature available that indicates episodic memory dysfunction in PTSD patients (Brewin, 2014; Dere et al., 2010; Isaac et al., 2006; Moradi et al., 2008) these findings are predominantly based on studies using tasks which do not necessarily capture the whole complexity of the episodic memory concept (Brewin et al., 2007; Isaac et al., 2006; Pause et al., 2010, 2013; Zlomuzica et al., 2014).

Apart from the remembrance of past experiences, the episodic

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memory concept involves the ability to perform mental time travel (MTT), to execute episodic future thinking and to establish prospective memories (Blix and Brennen, 2011; Breeden et al., 2016; Brown et al., 2014; Suddendorf, 2013; Suddendorf and Corballis, 1997). MTT is defined as the ability to recollect past events from episodic memory (MTT into the past) and to anticipate or imagine events in the future (MTT into the future). From a biological perspective, MTT seems to have evolved to serve a) the optimization of decision-making processes, b) efficient problem solving, c) the preparation for future needs, and d) the formation of intentions to perform actions at a specific time point in the future (Breeden et al., 2016). It is evident that patients with impaired MTT function would encounter problems in their social and professional functioning. Indeed, there is evidence that PTSD patients show difficulties in planning and structuring everyday activities (Mehnert et al., 2010; Scignaro et al., 2011) and exhibit compromised social problem-solving abilities (Reich et al., 2015). However, it is unclear whether these difficulties can be attributed to impairments in MTT. Furthermore, very little work has been conducted to examine the integrity and functional significance of MTT, episodic future thinking and prospective memory in the context of PTSD (but see Kleim et al., 2014). Finally, the successful retrieval and use of specific personal experiences as a clue to solve anticipated future problems represents a central element of cognitive-behavioral treatment approaches for PTSD (Zlomuzica et al., 2014).

In order to examine these phenomena we developed a specific test for the utilization of episodic memories for solving problems, in the present and future, respectively. We used a VR environment to measure the ability to generate integrated memory for “what happened, where, and when” (Binder et al., 2015; Kinugawa et al., 2013; Pause et al., 2010, 2013; Zlomuzica et al., 2015). We tested PTSD patients and healthy controls in this VR-based episodic memory task as well as a newly developed clinical test for MTT, episodic future thinking, and prospective memory. The virtual reality episodic memory test (What-Where-When WWW Task) is based on the rationale of the episodic-like memory task we developed for rodents (e.g. Dere et al., 2005a, 2005b; Kart-Teke et al., 2006; Zlomuzica et al., 2007; reviewed in Binder et al., 2015), and was adapted to humans for computer-based testing (Kinugawa et al., 2013; Pause et al., 2010; Weber et al., 2014) and VR-based assessment (Zlomuzica et al., 2015). Interestingly, VR-based techniques have been increasingly used in the treatment of PTSD (Botella et al., 2015). Hence, investigating to which extent patients with PTSD and healthy subjects differ in their ability to perceive and process complex information in VR and disambiguate different contexts is of valuable interest.

In an attempt to overcome some of the previous methodological weaknesses when assessing mnemonic functions in PTSD (see Isaac et al., 2006), age, education and sex-matched healthy participants were used as controls. A complementary neuropsychological examination of attention and everyday memory capacity (Moradi et al., 1999) was also conducted.

2. Methods and materials

2.1. Participants

Twenty-one participants who fulfilled DSM-IV criteria for PTSD (4 males, 17 females) and 21 healthy controls (4 males, 17 females) without a psychiatric diagnosis participated in this study. The presence of an Axis-I diagnosis was determined for all participants by means of the Diagnostic Interview for Mental Disorders-short version (Mini-DIPS, Margraf, 1994). PTSD patients were recruited via board advertisements in two specialist treatment centers. Exclusion criteria for PTSD patients were: a) diagnosed comorbid psychotic disorder, b) personality disorder, c) history of head injury, and/or d) other neurological diseases. Other existing comorbid diagnoses were recorded. The majority of PTSD patients (86%) reported at least one comorbid disorder. The

following comorbid diagnoses (based on DSM-IV classification) were present: Mood disorders (N = 14), anxiety disorders (N = 13), somatoform disorders (N = 2), eating disorders (N = 2), and drug abuse disorders (N = 1). A great proportion of the PTSD patients reported receiving psychopharmacological medication, including antidepressants (N = 11), neuroleptics (N = 8), tranquilizers or sleep-inducing drugs (N = 5).

Healthy controls were recruited by newspaper advertisement and from different community job centers. PTSD patients and healthy controls were matched by age, sex and education.

All participants were reimbursed with 35 Euro for their participation. All experimental procedures were approved by the local ethical committee of the Ruhr-University of Bochum, Germany. Experiments were conducted according to the guidelines of the declaration of Helsinki.

2.2. Clinical measures and other questionnaires

Each participant completed a set of specific clinical questionnaires: (i) The Impact of Event Scale-Revised (IES-R; (Weiss and Marmar, 1997); German version: (Maerker and Schützwohl, 1998) to capture trauma specific symptoms in both PTSD patients and healthy controls. (ii) The Posttraumatic Diagnostic Scale (PDS; (Foa, 1995); German version: (Ehlers et al., 1996) which consists of 49 items assessing PTSD symptom severity according to DSM-IV criteria. The PDS adds up to four subscales including intrusion, avoidance and arousal symptoms and the level of symptom severity. Specific cut-off scores in the PDS allow a classification of PTSD severity (i.e. a total score of ≤ 10 indicates mild, scores between 11 and 35 moderate, and scores ≥ 36 severe PTSD; (Griesel et al., 2006). (iii) Selected items from the Depression Anxiety Stress Scales (DASS; (Velten et al., 2014) were used to gather information on trait depression, anxiety and stress tension levels. (iv) The FERUS questionnaire (“Fragebogen zur Erfassung von Ressourcen und Selbstmanagementfähigkeiten” (Jack, 2007) was administered to assess self-reported personal resources and self-management skills. Subscales from the FERUS questionnaire are related to self-efficacy and coping, i.e., concepts which are closely linked to episodic memory performance and self-management skills (see Brown et al., 2012). Other subscales measure motivation to change behavior, self-observation, self-verbalization, hope, and social support. (v) Participants' sense of involvement in VR (VR) was measured with the Igroup Presence Questionnaire (IPQ; Schubert et al., 2001). The IPQ consists of 14 items assessing spatial presence, involvement, experienced realism, and general presence in VR.

2.3. General procedure

The general procedure is outlined in Fig. 1. Upon arrival, each participant was informed about the putative content of the study and the general procedure. Thereafter, informed consent was signed and each participant was asked to complete a set of standardized questionnaires including demographic information, clinical measures and other questionnaires. Also, participants completed the D2 test of attention and were then told that they would participate in an experiment investigating “visual attention and navigation in VR”. No explicit instruction was given about the exact purpose of the experiment. Most importantly, the participants were not explicitly instructed to retain any information presented during the course of the experiment or that a memory test would be performed afterwards. Before the actual experiment started, participants were asked to rate their emotional state on a visual analogue scale. Subsequently they were familiarized with the VR task during a 5 min training phase. Here, events different from those used later in the actual experiments were presented and the participants had the opportunity to actively move and explore the VR environment.

Each participant performed 2 consecutive walkthroughs in a virtual

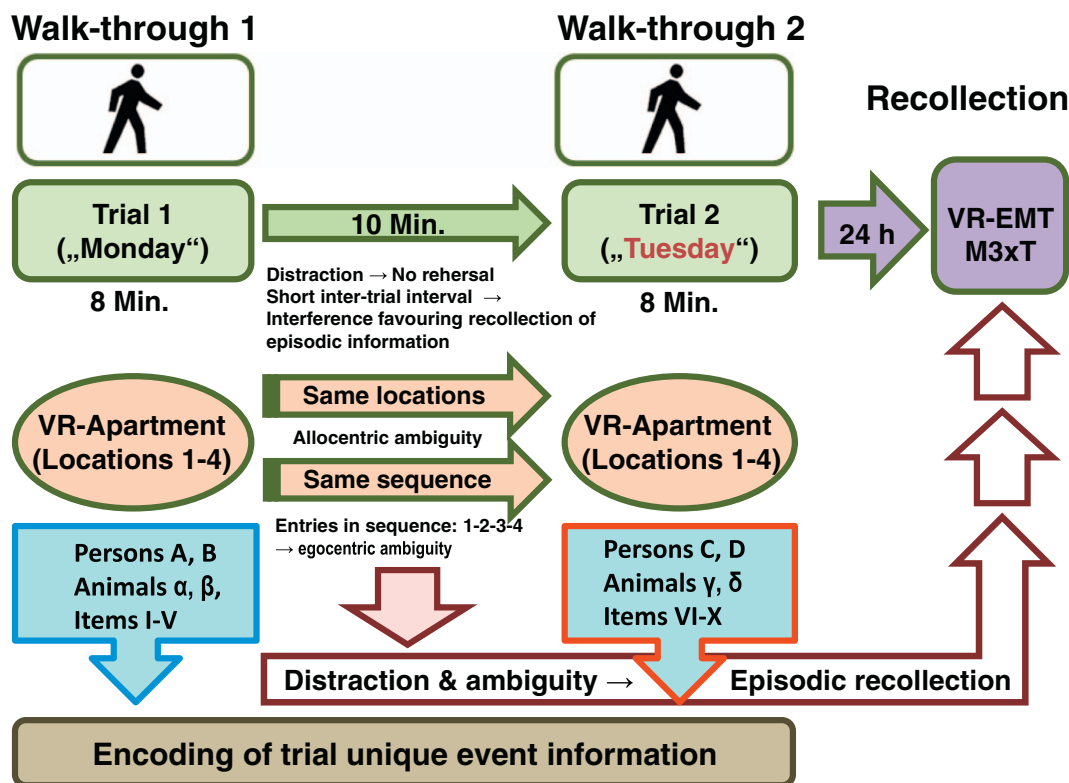


Fig. 1. General scheme of the VR-EMT experimental design. Participants performed two walk-throughs in a VR-apartment with 4 locations (rooms) that they explored in the same sequence (1-2-3-4) and for a comparable time (120 s maximum per room). After walkthrough 1 participants had to perform a distractor task of 10 min duration (questionnaires). The distractor task, short inter-trial interval, and the identical locations and sequences of entries into the 4 rooms prevented the rehearsal of information and created a high level of ambiguity that favour the recollection of episodic information during the recollection test performed 24 h later.

environment. The walk-throughs had a maximal duration of 8 min. The inter-walk-through interval was set at 10 min. Accordingly, the entire test was performed within 26 min. Thereafter, participants were informed that the experimental procedure will be continued 24 h later. Approximately 24 h later, participants were subjected to the retrieval phase during which the VR Episodic Memory Test (VR-EMT) and the Mental time travel test (M3xT) were conducted. After an additional delay, the Rivermead Behavioral Memory Test (RBMT) was administered and the participants' experience with playing video-games was noted.

2.4. Emotional arousal and activation during encoding and retrieval

In order to determine the level of emotional arousal and activation prior to encoding and retrieval (on day 1 and day 2), each participant completed paper-and-pencil visual analogue scales with the anchors 'absolutely not anxious' versus 'very anxious', 'absolutely not happy' versus 'very happy', 'absolutely not negatively aroused' versus 'very negatively aroused' and 'absolutely not positively aroused' versus 'very positively aroused' (according to Zlomuzica et al., 2015).

2.5. Encoding in the VR environment

Visual items from the software "Half-Life 2" were used to design the VR environment. The VR environment was presented on a 16 in. monitor. During two VR walk-throughs which constituted the episodic information encoding phase, participants were instructed to carefully explore a VR apartment (see Fig. 2). The procedure was repeated in the same manner on both walk-throughs, yet a delay of 10 min between trials was imposed, during which participants filled in another set of questionnaires. The two walk-throughs were named "Monday" and "Tuesday" (displayed for the entire period of each walk-through in the

corner of the monitor). Each walk-through involved two different persons, two different animals, and five distinct items, while none of these items were visually or thematically related to each other. Furthermore, none of the items were repeatedly presented during the two walk-throughs. During both "walk-throughs", items were presented at specific locations within the VR apartment. Four distinct rooms served as locations. Participants had to navigate using key pads and were instructed to explore freely each of the 4 rooms in the VR apartment for a maximum of 120 s. In each room, participants were instructed to attend the items and persons and explore these carefully. After 120 s had elapsed, the experimenter reminded them to move to the next room. Participants from both entered each of the rooms in the same order (Presentation order: Sequence of room entries: 1-2-3-4). Room numbers were clearly indicated at the respective door at the entrance (see Fig. 2C). The order of room exploration remained constant for all participants during both walk-throughs. However, the sequence of presentation related to the two walk-throughs was balanced across the groups; i.e., one half of the participants in each group first received a specific scenario labeled as "Monday" while the other half first received the other scenario labeled as "Monday" and vice versa. Both, the events and items as well as the spatial location varied across the two walk-throughs.

2.6. VR episodic memory test (VR-EMT)

A paper-pencil version of the VR-EMT was used as the retrieval test. Correct performance in the VR-EMT was operationalized as the capacity to remember and bind WWW features associated with a particular event. Each question in the VR-EMT was designed to measure the participants capability to remember which item (WHAT) was presented at which specific location (i.e. room, the WHERE component) and at which specific time point (i.e. day, the WHEN component). A total sum

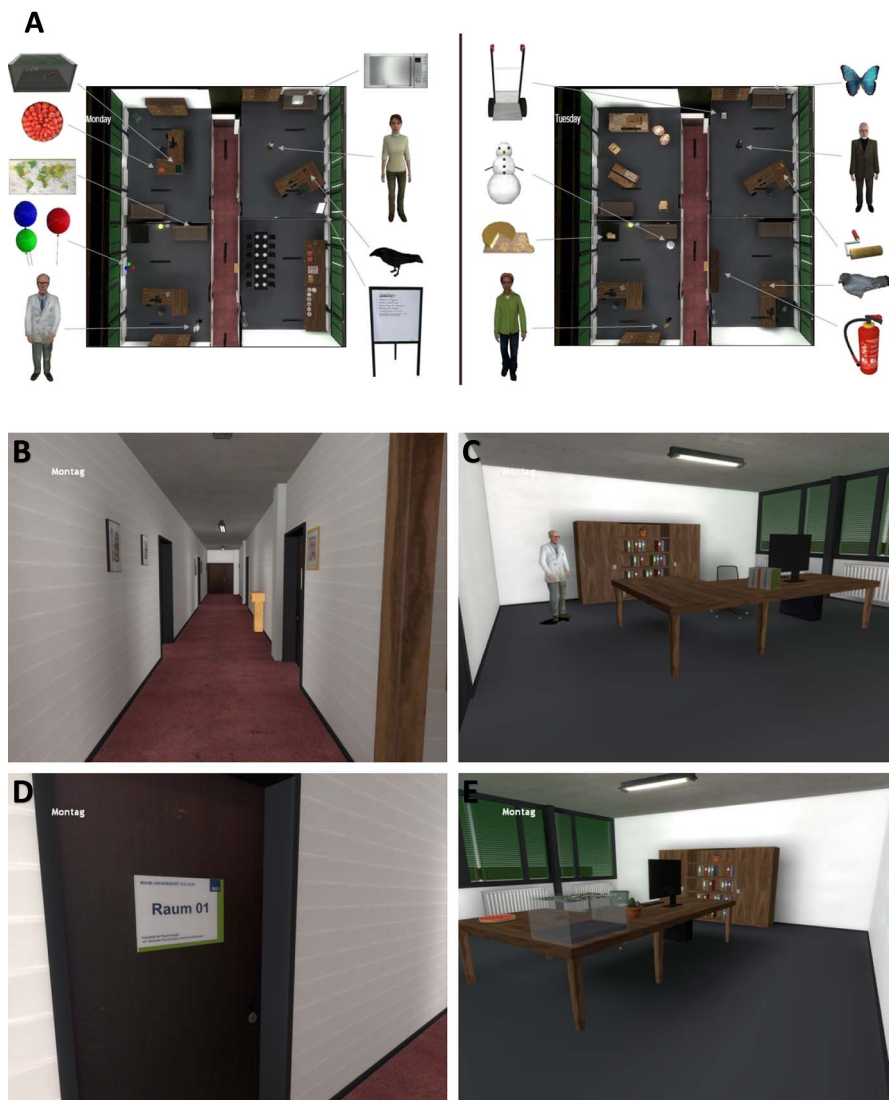


Fig. 2. (A–E). Episodic memory formation in the virtual environment. (A) Scheme of the VR-apartment and the stimulus items presented in the 4 rooms. (B–E) Virtual reality view of the (B) hallway, the rooms (C) and the specific items presented (D–E) from the perspective of the participant.

score of 18 was possible. A total of 18 questions were generated aimed to specifically measure the integrative component which is central to episodic memory functions (Kinugawa et al., 2013; Zlomuzica et al., 2015), but see Pause et al. (2013).

Three question categories were used. The categories differed with respect to the missing component which had to be remembered to correctly answer the question. Hence, each of the question categories already contained information on 2 of the 3 components while the participants had to indicate the missing component.

For instance, 6 questions contained information about a person, an animal or a specific item (WHAT component, e.g. a butterfly) and the time point (WHEN component, e.g. Monday) related to these specific items. The participants had to indicate the missing component: in this case provide the WHERE information, e.g. the room number. For example: “Monday, you encountered a butterfly. In which room did you notice the butterfly?”. While in the present example the WHERE information was the missing component, the 2 other question categories asked participants to provide the WHAT (six questions) or WHEN (six questions) information as the missing component.

2.7. Mental time travel test (M3xT)

The rationale of the M3xT was to examine whether PTSD patients show alterations in MTT functions including the capability to utilize or

employ information from episodic memory to solve current problems or to prepare for a future need (Atance and O'Neill, 2001; Breeden et al., 2016; Suddendorf, 2013). We therefore generated 12 questions which measure not only the participant's ability to remember WWW features from a specific event (similar to the VR-EMT version) but also the ability to use episodic memories for solving particular problems (i.e. planning actions in the future). Similar to the VR-EMT, the M3xT was presented as a paper-pencil test and contained 3 different categories of questions. For each category, participants had to read a specific context story and were requested to imagine themselves solving the problem posed in that particular context story. Each context story contained a specific instruction which had to be executed to accurately solve a specific problem.

In the first category of questions, participants were told that a specific person (e.g., a man in a suit) from the walk-through on Monday is celebrating his birthday and that a specific item (e.g., a distinct poster) will serve as the birthday present. Thereafter, an outline of the VR apartment was presented and participants were asked to draw a route indicating how to “bring the specific item (poster) to the particular person (man in the suit)”. Thus, apart from remembering the missing component (in this case WHERE) as requested during the VR-EMT, in the M3xT participants had to recall two distinct items (locations) from episodic memory (where was the man located and where was the poster located), use this information to execute an appropriate

action (in this case drawing a route between the two locations) that would solve the potential problem.

The second category of questions in the M3xT differed with respect to the missing memory component and the action to be executed. For instance, participants were told to imagine that a specific event takes place (e.g., a birthday party) and that they would need a special item from a particular room (e.g., room # 3) and a particular day (e.g., Monday). Here, participants had to remember the potential items from the specified context (since WHAT represents the missing component) and had to further infer which of these potential items would fulfill the required criteria for the imagined scenario (e.g., to prepare a birthday party).

Finally, in the third question category a context story in which WHEN was the missing component had to be remembered. Participants were told to imagine that a specific action had to be performed (e.g., painting the walls in the apartment) and that specific items (e.g., a paint roller from room #3) are needed. Here, participants were asked to indicate on which day (Monday or Tuesday) they would have to memorize to pick up the paint roller. The third question category thus tested the patient's ability to use episodic memories to form a prospective memory that is the intention to perform a certain action at a specific time and location in the future (reviewed in Breeden et al., 2016).

Prior to the test, the experimenter explained the rationale of the test and provided concrete examples how to solve the problems posed. Each of the question categories contained four context stories yielding a total sum score of 12.

2.8. Rivermead behavioral memory test (RBMT)

To cross-validate our VR-EMT and M3xT tests, we contrasted the performance of both patients and controls in the VR-EMT and M3xT tests with their performance in another neuropsychological test of episodic memory, the RBMT (Wilson et al., 1989); German version: (Beckers et al., 1992). The RBMT consists of 12 subtests, all of which measure recognition or recall of information highly related to everyday situations. Subtests refer to knowledge of the date, orientation to time and place, immediate and delayed memory for a name, face, picture, story or a route, as well as prospective memory capabilities (i.e., remembering an appointment). For each of the subtests, a standardized profile score of 0 (abnormal response), 1 (borderline response), or 2 (normal response) could be achieved leading to a standardized total score ranging from 0 to 24.

2.9. D2 test of attention

The D2 Test of attention was administered prior to the VR-EMT walk-through phase on the first day of the experiment. Participants were asked to cross out specifically marked target letters (each d underlined with two dashes) out of distractors within a maximum of 20 s per line (with 14 lines in total). For each participant, a standardized concentration performance score (SKL) was calculated as follows: SKL = number of correct responses minus number of confusions. The SKL is supposed to represent a robust and reliable measure of individual attention and concentration ability (Brickenkamp, 1994).

3. Results

3.1. Sample characteristics

As shown in Table 1, groups were matched in terms of age, gender distribution or level of education. As expected, PTSD patients experienced significantly more trauma events ($M_{PTSD} = 3.9$ [$SD = 2.1$], $M_{controls} = 0.7$ [$SD = 0.9$], $F(1,40) = 41.41$; $p < 0.001$) and reported more repeated traumas than healthy controls ($N = 16$ in the PTSD group versus $N = 2$ in the control sample). The PTSD group also showed higher scores of intrusion, avoidance and arousal symptoms

obtained with the IES ($ps < 0.001$) and PDS questionnaire ($ps < 0.001$), respectively. PDS symptom severity scores ranged from 10 to 46 ($M = 30$, $SD = 10.3$) in the PTSD group and from 0 to 14 in healthy controls ($M = 1.9$, $SD = 3.5$, $F(1,40) = 140.61$, $p < 0.001$, see Table 1). Furthermore, groups differed with respect to depression, anxiety and stress tension levels, all of which were significantly higher in PTSD patients relative to healthy controls ($ps < 0.001$, Table 1).

There was no difference between the groups in terms of experienced realism ($F(1,40) < 1$, $p = 0.801$), spatial presence ($F(1,40) < 1$, $p = 0.837$), involvement ($F(1,40) < 1$, $p = 0.532$), and global presence ($F(1,40) = 2.4$, $p = 0.129$) during the VR walk-throughs as evidenced by the IPQ. However, PTSD patients obtained lower SKL scores in the d2 attention test suggesting a diminished concentration performance in PTSD patients as compared to healthy controls ($M_{controls} = 183$ [$SD = 44$], $M_{PTSD} = 153$ [$SD = 34$], $F(1,40) = 6.14$; $p < 0.05$).

3.2. Episodic memory and mental time travel

To determine group differences in VR-EMT and M3xT, a MANOVA with group as between-subjects factor and VR-EMT and M3xT scores as dependent variables was conducted. Homogeneity of variances was not violated ($F_s < 1$, $ps > 0.46$, Levene-test) and testing for the equality of covariance matrices was not significant ($F < 1$, $p > 0.822$, Box-test). Using Hotelling's trace statistics, we found a significant main effect of group, $T = 0.25$, $F(2,39) = 4.94$, $p = 0.012$, $\eta^2 = 0.202$. Separate univariate ANOVAs revealed a poorer performance of the PTSD group, both in the VR-EMT ($M_{PTSD} = 7.52$ [$SD = 2.73$], $M_{controls} = 9.71$ [$SD = 3.35$], $F(1,40) = 5.4$, $p = 0.025$, $\eta^2 = 0.119$) and M3xT ($M_{PTSD} = 5.02$ [$SD = 2.23$], $M_{controls} = 7.31$ [$SD = 2.44$], $F(1,40) = 10.02$, $p = 0.003$, $\eta^2 = 0.2$).

Since PTSD patients showed lower scores in the d2 attention test, diminished concentration performance might have contributed to the observed group differences in VR-EMT and M3xT performance. We therefore performed a hierarchical regression analysis to determine the relationship between PTSD diagnosis and concentration deficits on the patients' performance in the VR-EMT and M3xT. The standardized concentration performance score (SKL) was entered at step 1 into the hierarchical regression analysis and group variable (PTSD patients versus healthy controls) was entered at step 2.

Concentration performance explained a significant amount of variance in the VR-EMT, $F(1,40) = 6.56$, $p < 0.05$; $R^2 = 0.14$; adjusted $R^2 = 0.12$. Although the model remained significant, the inclusion of group at the second step did not increase the amount of variance explained by the model considerably, $F(2,39) = 4.6$; $p < 0.05$; $R^2 = 0.19$; adjusted $R^2 = 0.15$, change in R^2 : $p = 0.13$. These results suggest that differences in concentration capacity contributed to the group differences in VR-EMT performance. However, differences in concentration capacity explain only 14% of the variance in the VR-EMT scores, indicating that the episodic memory impairment in the PTSD group is not only a secondary effect of concentration problems.

For performance in the M3xT, concentration scores also explained a significant part of the variance observed, $F(1,40) = 4.64$, $p < 0.05$; $R^2 = 0.10$; adjusted $R^2 = 0.08$. In contrast to the VR-EMT hierarchical regression analysis presented above, the inclusion of the factor group in step 2 significantly increased the proportion of variance explained, $F(2,39) = 5.81$; $p < 0.01$; $R^2 = 0.23$; adjusted $R^2 = 0.19$, change in R^2 : $p < 0.05$.

These results indicate that differences in the VR-EMT and M3xT performance between PTSD patients and healthy controls cannot be entirely attributed to a diminished concentration capacity in the PTSD group. Altogether, our results suggest that episodic memory formation and MTT is compromised in PTSD patients.

To determine whether the VR-EMT and/or M3xT deficits of the PTSD patients were related to a selective impairment in encoding and memorizing specific information categories such as item, temporal or

Table 1
Demographics and clinical questionnaire measures.

Variables	PTSD patients (N = 21)			Controls (N = 21)			p-Value
	M (SD)	Min	Max	M (SD)	Min	Max	
Age in years	34.6 (11.9)	18	55	34.2 (11.8)	18	53	0.92
Gender (% female)	81			81			1
Level of education ^a	2 (1)	0	4	2.1 (1)	0	4	0.65
Depression Anxiety Stress Scale (DASS)							
Depression	11.9 (5.6)	2	20	1.4 (1.6)	0	6	< 0.001
Anxiety	9.2 (4.4)	3	16	0.6 (0.9)	0	3	< 0.001
Stress	12.9 (5.1)	1	21	3.3 (2.9)	0	9	< 0.001
Self-management Skills (FERUS)							
Coping	30.9 (7.6)	14	46	44.1 (6.7)	29	57	< 0.001
Self-efficacy	21.8 (6.3)	12	38	35.6 (4.6)	24	43	< 0.001
Self-observation	20.7 (4.8)	11	30	25.3 (5.5)	16	33	< 0.01
Self-verbalization	13.7 (4.4)	8	26	20.4 (4.4)	12	28	< 0.001
Social support	33.6 (11.2)	16	50	46.1 (4)	38	50	< 0.001
Hope	28.1 (10.4)	13	46	41 (5.7)	26	50	< 0.001
Motivation for change	49.9 (9)	24	60	24.1 (10.7)	12	47	< 0.001
Global score	198.6 (35.4)	111	267	236.6 (29.9)	164	293	< 0.001
Impact of Event Scale (IES)							
Intrusions	22.8 (6.5)	9	35	2.1 (3.7)	0	10	< 0.001
Avoidance	19.8 (7.4)	0	31	3.5 (7.2)	0	23	< 0.001
Arousal	19.8 (8.1)	3	31	1.5 (2.2)	0	6	< 0.001
Posttraumatic Diagnostic Scale (PDS)							
Intrusions	9.1 (3.7)	3	15	0.3 (1)	0	4	< 0.001
Avoidance	11.9 (4.8)	2	20	0.8 (2)	0	9	< 0.001
Arousal	9.1 (3.5)	4	15	0.8 (1.2)	0	3	< 0.001
Symptom Severity	30 (10.3)	10	46	1.9 (3.5)	0	14	< 0.001
Group Presence Questionnaire (IPQ)							
Realness	7.5 (4.7)	0	17	5.5 (3.6)	0	12	0.13
Spatial presence	12.1 (7.5)	0	23	12.6 (5.8)	0	23	0.84
Involvement	10.6 (6.4)	0	22	9.4 (6.4)	1	24	0.53
Global item	2.4 (2)	0	6	2.2 (1.7)	0	5	0.8

Note. Standard deviations are given in parentheses. Continuous variables were analyzed using univariate ANOVAs, $F(1,40)$; categorical variables were analyzed using chi-square-tests. All p -values are two-tailed.

^a Level of education was scored on a scale ranging from 0 (primary school) to 4 (university degree).

spatial information, the three question categories that were specific to the ability to recollect WHAT, WHERE or WHEN information were analyzed separately.

Two mixed 2×3 ANOVAs were calculated, one for VR-EMT and a separate one for the M3xT task. Here, the three performance scores related to the three question categories WHAT, WHERE or WHEN served as within-subject factors while group was entered as the between-subjects factor.

In line with MANOVA results reported above, analyses for the VR-EMT revealed a main effect of group, $F(1,40) = 5.4$, $p < 0.025$, $\eta^2 = 0.119$, indicating poorer overall performance on the VR-EMT by PTSD patients. There was a main effect of question category ($M_{what} = 1.6$ [$SD = 1.3$], $M_{where} = 2.9$ [$SD = 1.4$], $M_{when} = 4.1$ [$SD = 1.7$], $F(2,39) = 54.3$, $p < 0.001$, $\eta^2 = 0.736$.) and a significant group \times question category interaction ($F(2,39) = 5.37$, $p = 0.009$, $\eta^2 = 0.216$). Simple effects for within-group analyses indicated that in both groups, WHEN ($ps < 0.001$) and WHERE scores ($ps < 0.001$) were significantly higher as compared to WHAT scores. Most importantly, between-group analyses revealed that PTSD patients had lower WHAT ($F(1,40) = 4.19$, $p < 0.047$, $\eta^2 = 0.095$) and WHEN scores ($F(1,40) = 11.46$, $p = 0.002$, $\eta^2 = 0.223$) as compared to healthy controls. No significant difference between groups was found for the WHERE scores ($p = 0.74$) (see Fig. 3).

In line with the results of the VR-EMT, a more detailed analysis of the M3xT data revealed a main effect of group, $F(1,40) = 10.02$, $p = 0.003$, $\eta^2 = 0.2$, with overall poorer performance of the PTSD group on the M3xT. Also, there was a main effect of question category ($M_{what} = 1.6$ [$SD = 1.1$], $M_{where} = 1.9$ [$SD = 1$], $M_{when} = 2.6$ [$SD = 1.1$], $F(2,39) = 18.12$, $p < 0.001$, $\eta^2 = 0.141$). Simple effects indicated that groups performed best on the question category referring to spatial information (WHERE; $ps < 0.001$), but memory performance

for the remaining categories (WHAT and WHEN) was similar ($p = 0.482$). Furthermore, there was a trend towards a significant interaction between group and question category, $F(2,39) = 3.21$, $p = 0.051$, $\eta^2 = 0.141$. Simple effect analyses suggested performance of the PTSD patients was inferior relative to healthy controls for the WHAT ($F(1,40) = 10.21$, $p = 0.003$, $\eta^2 = 0.203$), and WHEN scores ($F(1,40) = 8.38$, $p = 0.006$, $\eta^2 = 0.173$), but no group difference emerged with respect to the WHERE scores ($p = 0.218$; see Fig. 3).

3.3. RBMT

The groups' performance in the RBMT was analyzed by means of a one-way ANOVA with group as the between-subjects factor and total performance score as the dependent variable. A main effect of group was found ($M_{PTSD} = 19.5$ [$SD = 3$], $M_{controls} = 21.4$ [$SD = 2.7$], $F(1,40) = 4.64$, $p = 0.037$, $\eta^2 = 0.104$), indicating a poorer overall performance of the PTSD group as compared to healthy controls.

In order to determine the relationship between the ability to concentrate and RBMT performance, we performed a hierarchical regression analysis. Performance score in the d2 attention test (SKL-score) was entered at step 1 into the hierarchical regression analysis model and the factor group was entered at step 2. The RBMT total performance score constituted the dependent variable. Concentration capacity explained a significant amount of variance in RBMT performance ($F(1,40) = 7.51$; $p < 0.01$; $R^2 = 0.16$; adjusted $R^2 = 0.14$). Although the model remained significant, the inclusion of the factor group at step 2 into the model failed to increase the amount of the variance explained significantly ($F(2,39) = 4.71$, $p < 0.05$, $R^2 = 0.19$; adjusted $R^2 = 0.15$; change in R^2 , $p = 0.19$), suggesting that alterations in concentration capacity are likely to have contributed to the group differences in RBMT performance.

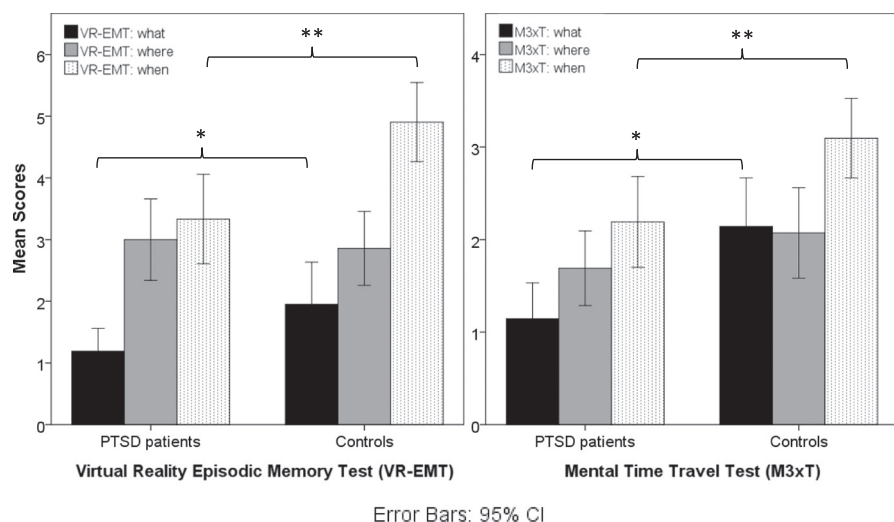


Fig. 3. Performance on the different question categories in the VR-EMT and the M3xT for each group. * denote significant effects, with $**p < 0.01$, $***p < 0.05$. Error bars represent 95% confidence intervals.

Table 2

Mean standardized profile scores and total score in the RBMT for PTSD patients and controls.

RBMT subtests	PTSD patients	Controls	U	p
Names	1.24 (0.94)	1.33 (0.97)	206.5	n.s.
Belongings	1.52 (0.81)	1.71 (0.46)	208.5	n.s.
Appointment	1.71 (0.46)	1.86 (0.36)	189	n.s.
Pictures	1.95 (0.22)	1.81 (0.40)	189	n.s.
Immediate route recall	1.71 (0.46)	1.81 (0.51)	192	n.s.
Delayed route recall	1.76 (0.44)	1.71 (0.51)	218	n.s.
Message	1.14 (0.79)	1.57 (0.68)	153	n.s.
Orientation	1.86 (0.36)	1.95 (0.22)	199.5	n.s.
Date	1.86 (0.48)	2 (0)	199.5	n.s.
Face recognition	1.67 (0.48)	1.67 (0.66)	206.5	n.s.
Immediate story recall	1.38 (0.74)	1.95 (0.22)	124.5	0.036
Delayed story recall	1.67 (0.66)	2 (2)	168	n.s.
Standardized Profile Score total	19.48 (3.01)	21.38 (2.71)	F	p
			4.64	0.037

Note. Standard deviations are given in parentheses. Standardized profile scores for subtests were analyzed using Mann-Whitney U tests, the standardized profile total score was analyzed using univariate ANOVA, $F(1,40)$.

We further assessed whether the performance of PTSD group in certain subtests of the RBMT was significantly different from that of healthy controls. For this purpose a standardized profile score (scores ranged from of 0 to 2; see methods section) was assigned to each participant and subtest. Group differences in mean performance scores in

the respective subtests were analyzed with multiple Mann-Whitney tests and Bonferroni correction was used to reduce the probability for making a type-I error. Except for a significantly lower performance score in the PTSD group in the subtest “immediate story recall” ($U = 124.5$, $z = -3.14$, $p = 0.036$) no other significant group differences emerged ($ps > 0.576$; see Table 2).

3.4. Emotional arousal and activation during encoding and retrieval

Differences in emotional states and arousal level prior to encoding (day 1) and prior to retrieval (day 2) were analyzed using a 2 (group) \times 2 (assessment time) \times 4 (emotional state: anxious, happy, negatively aroused, positively aroused) mixed design ANOVA. The Mauchly-Test indicated that the assumption of sphericity had been violated for the within-subjects factor emotional state, $\chi^2(5) = 27.46$; $p < 0.001$. Thus, results concerning this factor were corrected using Greenhouse-Geisser estimates of sphericity ($\epsilon = 0.67$). There was a significant main effect of emotional state, $F(2.01,80.41) = 29.47$; $p < 0.001$; $\eta^2 = 0.42$, and a significant emotional state \times group interaction, $F(2.01,80.41) = 10.86$; $p < 0.001$; $\eta^2 = 0.21$. In particular, PTSD patients demonstrated higher anxiousness levels, $F(1,40) = 5.25$; $p < 0.05$; $\eta^2 = 0.12$, significantly lower level of happiness, $F(1,40) = 24.1$; $p < 0.001$; $\eta^2 = 0.38$, and positive arousal, $F(1,40) = 6.46$; $p < 0.05$; $\eta^2 = 0.14$ (see Fig. 4).

In addition, a significant main effect of time, $F(1,40) = 9.72$, $p < 0.01$; $\eta^2 = 0.2$, and a significant time \times emotional state

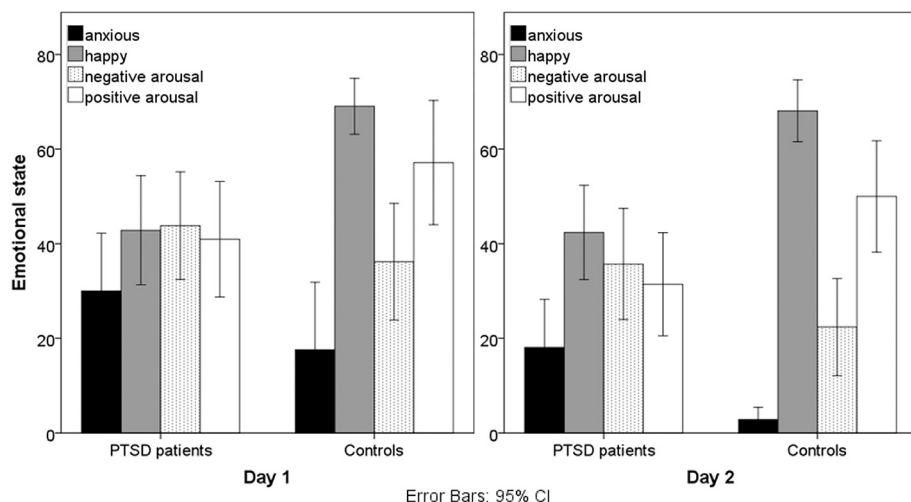


Fig. 4. Mean scores for the anxiousness, happiness, positive arousal and negative arousal per group on Day 1 (encoding) and Day 2 (retrieval) of testing. Error bars represent 95% confidence intervals.

Table 3
Person's correlations between performance scores in VR-EMT, M3xT and clinical measures separated by group.

Clinical measures/Episodic memory performance	Correlations for PTSD patients			Correlations for controls		
	VR-EMT	M3xT	RBMT	VR-EMT	M3xT	RBMT
Depression Anxiety Stress Scale (DASS)						
Depression	0.27 [−0.11; 0.55]	0.17 [−0.17; 0.50]	−0.65 [−0.87; −0.35]	−0.10 [−0.60; 0.41]	0.07 [−0.47; 0.47]	−0.18 [−0.63; 0.26]
Anxiety	0.10 [−0.30; 0.43]	−0.24 [−0.62; 0.13]	−0.49 [−0.74; −0.18]	−0.18 [−0.55; 0.13]	−0.16 [−0.50; 0.22]	−0.32 [−0.66; 0.02]
Stress	0.52 [0.07; 0.74]	0.42 [−0.07; 0.74]	0.02 [−0.46; 0.51]	−0.10 [−0.53; 0.49]	0.02 [−0.42; 0.46]	−0.37 [−0.75; 0.06]
Self-management Skills (FERUS)						
Coping	−0.11 [−0.64; 0.42]	−0.37 [−0.73; 0.22]	−0.31 [−0.69; 0.14]	0.10 [−0.40; 0.54]	0.12 [−0.25; 0.44]	0.15 [−0.39; 0.64]
Self-efficacy	−0.17 [−0.56; 0.24]	−0.35 [−0.69; 0.10]	−0.22 [−0.62; 0.17]	0.09 [−0.52; 0.59]	0.01 [−0.36 0.39]	0.39 [−0.16; 0.72]
Self-observation	0.01 [−0.43; 0.37]	−0.15 [−0.51; 0.30]	−0.22 [−0.70; 0.31]	−0.19 [−0.66; 0.36]	−0.16 [−0.48; 0.24]	0.21 [−0.24; 0.62]
Self-verbalization	−0.05 [−0.37; 0.27]	−0.25 [−0.52; 0.04]	−0.27 [−0.61; 0.04]	−0.13 [−0.63; 0.33]	−0.18 [−0.54; 0.20]	0.21 [−0.28; 0.60]
Social support	0.11 [−0.27; 0.50]	0.05 [−0.47; 0.40]	0.25 [−0.19; 0.66]	0.38 [−0.18; 0.76]	0.10 [−0.42; 0.56]	0.43 [−0.34; 0.81]
Hope	−0.09 [−0.44; 0.32]	−0.33 [−0.67; 0.18]	−0.06 [−0.51; 0.37]	0.20 [−0.52; 0.67]	0.01 [−0.44; 0.47]	0.49 [−0.11; 0.78]
Motivation for change	0.39 [0.06; 0.74]	0.13 [−0.26; 0.52]	0.004 [−0.58; 0.45]	−0.16 [−0.55; 0.28]	−0.04 [−0.43; 0.38]	0.03 [−0.44; 0.37]
Global Score	0.04 [−0.34; 0.42]	−0.24 [−0.50; 0.13]	−0.11 [−0.62; 0.33]	0.01 [−0.61; 0.54]	−0.03 [−0.39; 0.34]	0.33 [−0.25; 0.71]
Impact of Event Scale (IES)						
Intrusions	−0.11 [−0.61; 0.36]	−0.18 [−0.61; 0.22]	0.03 [−0.50; 0.52]	−0.19 [−0.55; 0.18]	−0.26 [−0.57; 0.11]	0.18 [−0.11; 0.41]
Avoidance	−0.16 [−0.49; 0.22]	−0.16 [−0.62; 0.39]	−0.09 [−0.50; 0.53]	−0.15 [−0.52; 0.24]	0.31 [−0.63; 0.17]	0.19 [−0.06; 0.40]
Arousal	0.04 [−0.56; 0.44]	−0.20 [−0.69; 0.32]	−0.35 [−0.70; 0.04]	−0.24 [−0.61; 0.14]	−0.54 [−0.78; −0.19]	0.21 [−0.20; 0.50]
Posttraumatic Diagnostic Scale (PDS)						
Intrusions	0.09 [−0.31; 0.43]	−0.12 [−0.57; 0.32]	−0.24 [−0.67; 0.26]	−0.20 [−0.49; −0.03]	−0.18 [−0.60; 0.06]	0.10 [−0.08; 0.27]
Avoidance	0.01 [−0.36; 0.34]	0.05 [−0.46; 0.49]	−0.36 [−0.70; 0.004]	−0.09 [−0.44; 0.33]	−0.33 [−0.62; 0.35]	0.10 [−0.14; 0.30]
Arousal	0.36 [−0.12; 0.67]	0.16 [−0.45; 0.60]	−0.30 [−0.65; 0.07]	−0.16 [−0.62; 0.26]	−0.19 [−0.65; 0.32]	0.28 [−0.02; 0.51]
Symptom Severity	0.16 [−0.26; 0.47]	0.04 [−0.50; 0.49]	−0.35 [−0.70; 0.06]	−0.16 [−0.54; 0.18]	−0.31 [−0.62; 0.27]	0.18 [−0.06; 0.41]

Note. Bootstrapped 95% Confidence Intervals (CIs) are given in square parentheses. Correlation coefficients with CIs that do not include zero are presented in bold letters.

interaction, $F(3,120) = 2.81$; $p < 0.05$; $\eta^2 = 0.07$ was found. Simple effects revealed that irrespective of group assignment, participants showed more anxiousness on day 1 relative to day 2, $F(1,40) = 10.65$; $p < 0.001$; $\eta^2 = 0.21$. In addition, participants from both groups scored higher on negative arousal at day 1 compared to day 2, $F(1,40) = 7.24$; $p < 0.01$; $\eta^2 = 0.15$ (see Fig. 4).

3.5. Correlations with clinical measures

In order to determine the relationship between VR-EMT, M3xT and RBMT performance and clinical measures (subscales from the DASS, FERUS, IES and PDS), bivariate correlation analyses were conducted for the PTSD and healthy control sample, separately (see Table 3). There was a positive correlation between performance on the VR-EMT and the DASS stress-subscale for patients, $r = 0.52$ [bootstrapped Confidence Interval; CI: 0.07; 0.74], but not for healthy controls, $r = -0.10$, [CI: -0.53; 0.49]. The difference between these correlations was statistically significant ($Z = 2.03$, $p = 0.021$). Additionally, there was a positive correlation between patients' VR-EMT performance and motivation to change as assessed with the FERUS questionnaire, $r = 0.39$ [CI: 0.06; 0.74]. This association was not found in healthy controls, $r = -0.16$ [CI: -0.55; 0.28], and the difference between these two correlation coefficients was significant ($Z = 1.72$, $p = 0.04$). An inverse correlation between performance on the M3xT and arousal scores as measured with the IES occurred for healthy controls, $r = -0.54$ [CI: -0.78; -0.19], but not for the PTSD sample, $r = -0.20$ [CI: -0.69; 0.32]. However, these correlations did not significantly differ from each other: $Z = 1.20$, $p = 0.114$. Finally, patients' performance on the RBMT was negatively related to the DASS depression-subscale, $r = -0.65$ [CI: -0.87; -0.35], as well as the DASS anxiety-subscale, $r = -0.49$, [CI: -0.74; -0.18]. These correlations were not evident in healthy controls (both CIs included zero; see Table 3). The correlation between RBMT and DASS-depression subscale was significantly higher in patients relative to controls ($Z = 1.78$, $p = 0.038$). Correlation coefficients for RBMT and DASS-anxiety were not significantly different between groups ($Z = 0.61$, $p = 0.270$). In Fig. 5 scatterplots and regression lines for all correlations reported are illustrated.

4. Discussion

In the present study, we used a novel VR-based approach to investigate episodic memory formation and MTT in patients with PTSD. Compared to healthy controls, PTSD patients exhibited deficits in remembering item and temporal information both in the episodic memory formation and MTT tests. Consequently, PTSD patients showed impairments in their capability to employ information from episodic memory to solve current or future problems. This is in line with a recent report (using autobiographical interviews) suggesting that both autobiographical memories and episodic future thinking in PTSD patients lacks episodic specificity (Brown et al., 2014). Further exploration is needed to clarify whether this lack in episodic specificity might be more pronounced for recalled or imagined positive as compared to negative events. In a recent study however, Kleim et al. (2014) used the autobiographic memory test (AMT) and asked PTSD patients to generate short descriptions of imagined future events in response to positive or negative cue words. PTSD patients imagined fewer specific future events in response to positive cue words, but performed comparable to healthy controls with regard to negative cue words. Another study however, found no differences between female PTSD patients and healthy controls in the specificity and temporal distribution of autobiographical memories and future-directed thoughts (Blix and Brennen, 2011).

These inconsistent observations might be related to the paradigms used to measure episodic memory function and MTT (but see Dere et al., 2010; Pause et al., 2013). In the present study we chose to induce and measure the formation of new episodic memories instead of using

the AMT or other tasks, which rather measure the ability to retrieve old episodic memories in a vivid, detailed and specific manner (Griffith et al., 2012; Pause et al., 2013; Zlomuzica et al., 2014). Furthermore, we used a VR-based environment to characterize to which extent impairments in episodic memory affect the memory for central event details, and/or spatio-temporal contextual elements (Binder et al., 2015; Zlomuzica et al., 2015). Most importantly, our approach allowed us to investigate the functional significance of altered episodic memory functions and MTT.

The virtual reality episodic memory test (What-Where-When Task) is based on the rationale of the episodic-like memory task we developed for rodents (e.g. Dere et al., 2005a, 2005b; Kart-Teke et al., 2006; Zlomuzica et al., 2007; reviewed in Binder et al., 2015), and was adapted to humans for computer-based testing (Kinugawa et al., 2013; Pause et al., 2010; Weber et al., 2014) and VR-based assessment (Zlomuzica et al., 2015).

Previous studies usually assessed autobiographical memory and MTT by means of an adapted version of the AMT (e.g. Kleim et al., 2014; Brown et al., 2013, 2014). The conventional procedure of such future-based AMT is to present a number of cue words and ask participants to generate personal past and future events upon stimulus presentation. The extent to which participants describe these events in detail (scored by an independent rater) is taken as a readout for the performance on the AMT. Whenever a participant is unable to generate a response, his/her response is scored as an 'omission'. The use of the AMT, however, bears a number of methodological difficulties which can contribute to differences in the calculation and interpretation of the results (summarized in Griffith et al., 2012; but see also Zlomuzica et al., for a detailed discussion). For example, the coding system of the AMT has been criticized as to whether it is suitable to capture the complexity of autobiographical episodic memories (Söderlund et al., 2014). Also, given that a limited number of classification labels exist, the rater might be subsequently „forced“ to rate or categorize a reported memory as either specific or general. Furthermore, the participant's performance on the AMT does not allow conclusions about how accurately the participant recollected their experiences (Zlomuzica et al., 2014) since there is no experimental procedure that probes memory accuracy. Similar to retrospective episodic memories the MTT has a constructive nature (Breedon et al., 2016; Dere et al., 2017). Some leading theories emphasize that episodic future thinking implicate a „mental reconstruction of earlier events“ (Suddendorf and Corballis, 2007; Suddendorf, 2013), the capability to maintain specific information related to these events (possibly by using the working memory system, see Dere et al., 2017) and the simulation of future scenes where information from the past is being used to solve a particular problem. We propose that the AMT cannot capture this complexity in full detail. However, instead of arguing that the AMT is inappropriate to assess MTT we rather propose that the task specific demands of our approach and the AMT procedure might only partially overlap. The present approach involves the reconstruction of previously encountered events in terms of their spatial and content information. In order to solve a particular problem during the task, participants need to recollect specific information which is embedded in a spatial context and presented at a specific time point. The task specific demands, which are crucial to perform adequately, might be strongly related to the concept of „scene reconstruction“ as proposed by Hassabis and Maguire (2007), which might be central to MTT in their proposed model. Here, the ability to form and maintain a mental representation of previously encountered scenarios with respect to their content and their spatial and temporal components is crucial to respond adequately to solve a particular problem. In contrast, performance on the AMT does not necessarily involve recollection of spatial and temporal components but rather the capability to imagine a personally relevant and specific scene, which is subsequently described in detail by using verbal and „vivid“ descriptions. Since the primary purpose of our approach was to examine a possible mechanism why PTSD patients exhibit difficulties in planning

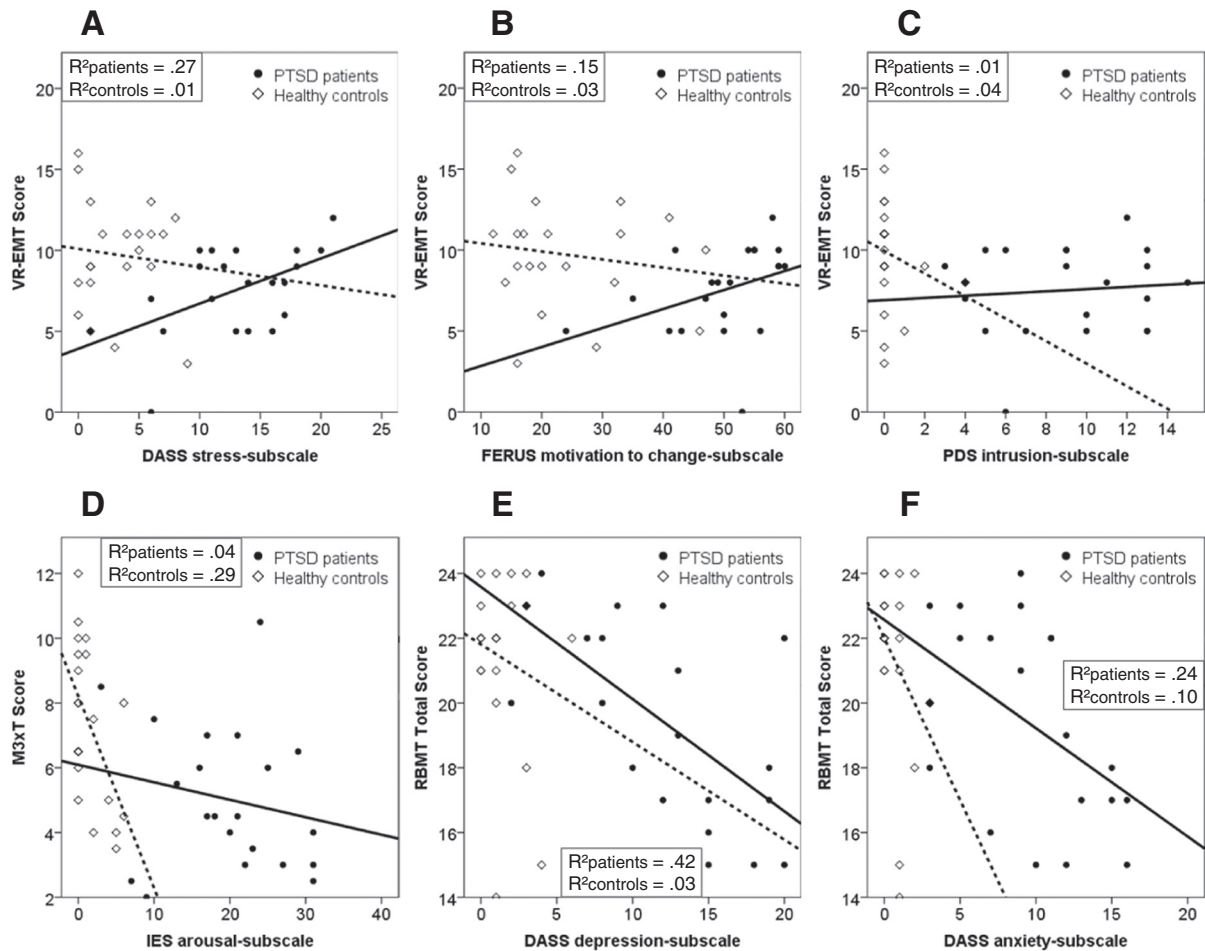


Fig. 5. Regression plots of performance scores in VR-EMT, M3xT and clinical measures separated by group. (A) – (C) association between VR-EMT performance and stress (stress subscale of the Depression Anxiety Stress Scales; DASS), motivation to change (“Fragebogen zur Erfassung von Ressourcen und Selbstmanagementfähigkeiten”; FERUS), and intrusions (Posttraumatic Diagnostic Scale; PDS), respectively (D) association between M3xT performance and arousal (Impact of Event Scale; IES); (E) – (F) association between RBMT performance and depression and anxiety (both measured by the DASS). Continuous lines and filled circles: PTSD patients; dashed lines and rhombuses: healthy controls; R^2 = percentage of explained variance.

and structuring everyday activities (Mehnert et al., 2010; Scrignaro et al., 2011) and to show compromised social problem-solving abilities (Reich et al., 2015), we prefer to use the VR-based tasks instead of the AMT.

To summarize, the present approach was designed in the context of a real-life scenario with the overall aim to examine whether difficulties in planning and problem-solving can be attributed to impairments in MTT and prospective memory. To overcome difficulties in the interpretation of the findings across different MTT tasks we might need more elaborated theoretical models describing this complex cognitive system as well as its underlying mechanisms in more detail (but see Suddendorf and Corballis, 2007; Suddendorf, 2013; Breeden et al., 2016; Dere et al., 2017; Hassabis and Maguire, 2007).

The VR-EMT task is based on several core characteristics of episodic memory formation and retrieval. It was designed to preclude the possibility that participants simply retrieve semantic what-where-when associations instead of recollecting episodic information. No explicit instruction to memorize information was given to the participants. Thus, the encoding of episodic information was unintentional, similar to the circumstances of episodic memory formation in everyday life (Dere et al., 2010; Pause et al., 2013; Zlomuzica et al., 2014). The encoding of episodic information (walk-through 1 and 2) occurred on one day within a very short period of only 26 min (8 min. walk-through 1 + 10 min. inter-trial-interval + 8 min. walk-through 2), while episodic information was recollected after a long delay of 24 h (Fig. 1).

Previous studies on episodic memory functions in PTSD patients (Isaac et al., 2006) predominantly used retention intervals of ≤ 30 min which does not qualify as long-term episodic memory (Pause et al., 2013). The short encoding time of 8 min. and the introduction of distraction tasks between the short inter-trial interval counteracts the formation and rehearsal of semantic what-where-when associations. Given that both walkthroughs were performed within 26 min, while recollection was performed after 24 h, makes it also unlikely that the temporal order (when information) of walkthroughs 1 and 2 could be inferred from simple familiarity judgments, based on the decay of memory strengths for the 2 walkthroughs. Moreover, the short inter-trial interval is very likely to induce memory interference, favoring a retrieval mode based on episodic recollection. In fact, only the recollection of episodic information would resolve this ambiguity.

Another important aspect of episodic memory is to keep track of different events happening in exactly the same location (Tulving, 2002). Given that different items were presented in the same location during walkthroughs 1 and 2, there is no singularity in a given item-room association. Thus, the information on the room alone will not help the participant to decide which items were encountered during a given walkthrough. Again, only the recollection of episodic information would resolve this type of contextual ambiguity. In conclusion, with respect to the nature of episodic memory formation and recollection, participants had to use episodic memory to successfully recall what items were presented in which room during a particular walkthrough.

The most effective treatment for PTSD is cognitive-behavioral therapy. A major aim of cognitive-behavioral interventions is to promote patient's capability to utilize specific skills to manage current and future social and emotional problems. This, however, is highly dependent on subject's capability to remember specific details from previous experiences as well as the ability to project oneself into the future and simulate novel events (Atance and O'Neill, 2001; Zlomuzica et al., 2014; Margraf and Zlomuzica, 2015). Our results indicate that these domains are affected in PTSD patients.

The convergent validity of our VR-EMT was tested in a cross-validation experiment using the RBMT (Moradi et al., 1999). The latter confirmed the results obtained with the VR-EMT and M3xT tests. In the RBMT, the PTSD patients showed poorer overall performance as compared to healthy controls. As expected, the VR-EMT and the RBMT scores were positively correlated in the healthy control sample, suggesting that both tests very likely to measure similar cognitive functions, including episodic memory. In contrast to previous studies on episodic memory in PTSD (Isaac et al., 2006), our sample of PTSD patients was matched to a healthy control group with respect to age, gender and education level, to exclude confounding effects of these variables on task performance.

The assessment of emotional arousal during encoding and retrieval of episodic information and MTT indicated that PTSD patients show higher levels of negative and lower levels of positive arousal relative to healthy controls. In healthy controls, VR-EMT and arousal scores were negatively correlated, while RBMT and subscale-scores from the FERUS questionnaire (which measures resources and self-management skills) were positively correlated. There was a positive correlation between performance on the VR-EMT and the DASS stress-subscale for PTSD patients, but not for healthy controls. Additionally, a correlation between RBMT and DASS-depression subscale in PTSD patients was found which was significantly higher relative to healthy controls.

These results are in line with the proposal that episodic memory formation is initiated by emotional status and that high level of arousal (as in the case of PTSD patients) interferes with episodic memory formation and retrieval (Dere et al., 2010; Pause et al., 2013; Wingenfeld et al., 2012; Zlomuzica et al., 2015). It would be interesting to know how the use of positive and trauma-related items embedded in the VR would affect the performance of PTSD patients in our task. It might be expected that PTSD patients would show a memory bias for information that accords with their negative interpretation of current or anticipated situations (Ehlers and Clark, 2000).

The observed deficits in MTT and prospective memory in PTSD might be strongly related to depression and anxiety symptoms which are common comorbidities of PTSD psychopathology. Emotions are an integral component of episodic memory formation, and the absence of emotional activation precludes the long-term storage of episodic memories (Dere et al., 2010; Pause et al., 2010, 2013). Thus, it is reasonable that changes in the level of anxious or depressive symptoms can indeed affect episodic memory formation. We have previously shown that experimental manipulation of negative and positive arousal indeed affects the remembrance of specific events in terms of what happened, where, and when (Zlomuzica et al., 2015). Previous findings in the domain of MTT and prospective memory provided rather unequivocal results regarding the link between depression/anxiety and prospective memory or MTT. While some of these studies did not find correlations between depression and MTT capabilities (Kleim et al., 2014), others reported correlations between depressive symptoms and distinct sub-components of PM (i.e. time-based PM, see Scott et al., 2016). Most importantly, patients with major depression (MD) seem to exhibit a similar pattern of deficits in these tasks (Li et al., 2013), indicating that depression and PTSD might indeed lead to comparable impairments in the capability to MTT and to remember specific details from future events. The literature on the association between anxiety and MTT and prospective memory function, however, is scarce and inconsistent (e.g. see Arnold et al., 2015; Harris and Menzies, 1999). While we did not

find any correlation between depression and anxiety scores and performance on the M3xT test, our design does not allow clear-cut conclusions as to whether depression and/or anxiety might mediate deficits in M3xT in PTSD patients. One way to dissociate the impact of depression and anxiety symptoms on distinct features of MTT and prospective memory (PM) in PTSD could be to employ larger patient samples and assess the correlation between PTSD symptoms and MTT/PM while controlling for levels of anxiety and depression. Nevertheless, again one needs to keep in mind that such an approach might not provide definite answers to the causal neuropsychological and neurobiological mechanisms underlying such observed deficits. In particular, diminished performance in the MTT task in PTSD might be related to diverse deficits in executive functions such as mental shifting and information updating (Miyake et al., 2000) or working memory capacity (Schoofs et al., 2008) which both can be impaired in PTSD (Aupperle et al., 2012; Moores et al., 2008). While these functions can remain relatively preserved in depression, depressive patients show alterations in other cognitive processes (e.g. allocation of attentional resources) which could equally lead to deficits in PM tasks and MTT (see Li et al., 2013, 2014). Likewise, while PTSD and depression rely on distinct neurobiological and neuroanatomical alterations the associated behavioral response pattern in tasks on MTT and PM might be similar. Thus, future studies need to disentangle which distinct neuropsychological and neurobiological dysfunction might drive observable deficits in MTT and PM in PTSD, relative to MD and anxiety. Such studies could profit from additional assessment of core neurocognitive functions in these patients, including well-selected neuropsychological tasks on executive function, selective attention and working memory capacity.

Specifically designed future studies might also provide more insights into the neurobiological mechanisms which underlie changes in episodic memory functions in the context of PTSD. Both the recollection of past events and the anticipation of future events critically depend on the integrity of the hippocampal formation (Tulving and Markowitsch, 1998). The hippocampal volume loss of PTSD patients is known to correlate with changes in hippocampal memory function (Tischler et al., 2006; Woodward et al., 2009) and PTSD symptom severity (Chalavi et al., 2015). However, it is not clear yet whether the hippocampal volume reduction itself represents a vulnerability which increases the risk to develop PTSD after trauma (Gilbertson et al., 2002), or whether the severe stress that is associated with traumatic event itself or the persistence of PTSD symptoms leads to the hippocampal volume loss (Chao et al., 2014; Hayes et al., 2011; Karl et al., 2006). Recent evidence suggests that damage to the hippocampus disrupts both the remembrance of very remote episodic memories and MTT capacity in healthy participants (Bartsch et al., 2011). However, no research exists that attempts to understand the contribution of hippocampal degeneration in PTSD to changes in episodic memory formation and MTT and the efficacy of therapeutic interventions on these alterations (Moustafa, 2013). Recently, it was shown that autobiographic memory specificity training can help to improve symptoms of PTSD (Moradi et al., 2014). Hence it would be valuable to examine whether a training version of our VR-based task for episodic memories and MTT might be an effective intervention for the treatment of PTSD and recovery from hippocampal volume loss in PTSD patients (Moustafa, 2013).

The relatively small sample size might limit the interpretation of our study. However, the sample size used in this study is comparable to similar studies from this field which utilized VR-based tasks (Tempesta et al., 2012), the RBMT (Moradi et al., 1999), MTT tasks (Brown et al., 2013, 2014), and/or prospective memory tasks (Glienne et al., 2017). To overcome limitations from previous studies, however, we included healthy subjects matched on age, sex, and education matched as a comparison group. In fact, some authors argued that these are major confounding variables when comparing episodic memory performance in PTSD patients relative to healthy controls (Isaac et al., 2006). As such, this should be considered as another advantage of our approach.

PTSD patients also showed deficits in attention that might have affected the encoding of episodic information, the utilization of recalled episodic information in the MTT test and performance in the RBMT. In fact, deficits in attention and concentration usually go along with declarative memory impairments in PTSD and have been reported in a number of studies (summarized in Hayes et al., 2012).

An association between attention deficits with impaired episodic memory performance has also been demonstrated in patients with Alzheimer's disease. Episodic memory and mental time travel deficits of Alzheimer patients are correlated with deficits in attention to relevant information of an episode (Kamkwala and Newhouse, 2017; Kirova et al., 2015). A recent theory on the evolution of mental time travel across species emphasizes the importance of attentional and working memory functions as the main prerequisites for MTT (Breedon et al., 2016; Dere et al., 2017). Findings of the present study have important implications for the understanding and treatment of episodic memory and mental time travel deficits in PTSD patients. For one, these deficits are likely to be correlated with attention and working memory deficits and the treatment of these deficits should include the training of both attention and working memory capacity. In future studies we plan to compare PTSD patients with and without prior attention and working memory training in the VR-EMT and MTT tasks.

5. Conclusions

In sum, our findings suggest that PTSD patients are impaired in the capacity to establish and utilize episodic memories. Furthermore, the PTSD patients showed deficits in MTT, which might account for impaired social and professional functioning. We suggest that cognitive behavior therapy in PTSD should include interventions that train attention and working memory and refine the ability to utilize episodic memories to solve problems. Another important outcome of cognitive behavior therapy in PTSD should be the training of the patients' ability to imagine and plan future activities and events.

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