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Virtual Reality Exposure Therapy for Armed Forces Veterans with Post-Traumatic Stress Disorder: A systematic review and focus group

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Abstract

Introduction: This study aims to determine the guidelines for designing a Virtual Reality – War Scenario program for Armed Forces veterans diagnosed with Post-Traumatic Stress Disorder.

Methods: This article encompasses two studies: Study 1, a systematic review of eleven articles indexed in the databases B-on, PubMed, Clinical trials and Cochrane Library; Study 2, a focus group of Portuguese armed forces veterans, discussed the outline of such a programme.

Results: A set of guidelines were identified as central and consensual, which should be included in the program. This type of program must have a realistic, multisensorial and interactive approach that allows veterans to re-adapt to their past, which is still so present. Virtual reality offers veterans with Post-Traumatic Stress Disorder unlimited opportunities, enhancing a personalized intervention.

Conclusion: The results support the use of VRET as an efficacious treatment for combat-related PTSD, but suggest nevertheless, VRET, as a co-creation process, requires more controlled and in-depth research on their clinical applicability.

Keywords: virtual reality; exposure therapy; post-traumatic stress disorder; military veterans.

Índice

1. Introduction

Post-Traumatic Stress Disorder (PTSD) falls into the class of stress-related traumas identified in the Diagnostic and Statistical Manual of Mental Disorders – 5th edition (American Psychiatric Association, 2014) and International Classification of Diseases (ICD-11). (1,2)

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), PTSD is considered a syndrome due to the complexity of its symptoms, which includes the presence of repeated and unwanted intrusive symptoms about an event (memories, dreams, flashbacks), persistent avoidance of the stimuli associated with it (thoughts, emotions, places), negative changes in cognition and mood (distorted cognition, beliefs or expectations) and significant changes in activation and reactivity (hypervigilance, difficulty in sleeping, irritable behavior). (3)

Post-traumatic stress disorder (PTSD) is a common disease, with prevalence rates in the general adult population of 6.8% in the United States and 0.6–6.7% in Europe (4,5). PTSD negatively impacts patients' daily lives and is associated with higher mortality risk (6).

The development of PTSD depends on numerous factors, such as an individual's psychological vulnerabilities, self-esteem, coping strategies, social and family support (7–9). It seems to be more severe and lasting when the stressful event is caused by humans or man-made artifacts (bombing, shooting, combat, etc.) (10)

These circumstances give this pathology the subjectivity that makes it different from individual to individual since what can be traumatic for one person may not be for another. (7)

Over the last decade's research has shown that events such as wars generate a higher probability of developing long-term PTSD. (11) Even for the ablest military personnel, war is one of the most challenging events to overcome. They are subject to physical, emotional, and mental wear and tear with possible consequences in the medium and long term. War is a fertile field thanks to the high risk of combat and the possible cruel and grotesque actions and exposure that the combatant committed and observed, as well as the death of comrades with which he related daily. These factors must be added to the stress of prolonged fatigue, food deprivation, poor hygiene and living conditions, and the prolonged absence of loved ones and family. (12,13)

This prolonged exposure to which the combatant is subjected tends to give rise to serious psychological adjustment problems. (12,13) For all these factors, it is necessary to create innovative and viable strategies for systematic monitoring so that the evolution and reduction of symptoms is a promising reality. (14,15)

There is a wide range of psychological treatments for Armed Forces veterans diagnosed with PTSD. Several studies document the efficacy of VR exposure therapy, which can simulate the physical presence in a real or imaginary environment, enabling exposure of the patient to the stressful environment. (16) Virtual reality programmes provide a better understanding of biopsychosocial factors that serve as information to prevent, evaluate, and treat PTSD, enabling the therapeutic effect to be increased, given the "presence" of the threatening stimulus. (17) Whatever the real world's limitations, VR can overcome them and generate a new reality. VR is no longer an abstract concept accessible only to video game enthusiasts but an ally in the therapeutic process. (18)

In this context, the Human-Computer interaction technologies bring more perspectives of using the virtual environment for people who suffer or have suffered different types of trauma. These areas can be contemplated in games with specific purposes to acquire new concepts and train or develop new skills. (19)

They have a significant advantage control over the stimuli, the possibility to repeat the exposure infinitely, and the unique option to simulate environments that challenge the limits of the daily environment, all of which allow the testing of different hypotheses on human behavior while diminishing the therapist's support. VR-based exposure can be accepted more quickly than traditional therapy because there is a "leap" from an office exposure to an in vivo exposure. Taking this "leap" offers a more palliative intervention that can reduce treatment dropout rates. All these features contribute to the implementation of VR as a method of therapeutic exposure. (20)

Simulations can also be classified by their degree of difficulty and repeatedly tried until correct learning is performed. Patients will face difficult situations in the VR environment more quickly than in real life. (21)

Furthermore, VR gives the therapist the ability to individualize the needs of the treatment, manipulate a more significant number of stimuli within the VR environment than in the real world and customize the context and sensory suggestions. The VR environment may also be adapted to a patient's fear hierarchy, i.e., creating a list of order points that cause anxiety on a scale from the lowest to the highest. Copious evidence shows that VR environments produce emotional, physiological and behavioral responses similar to those observed in real-life situations. (22)

The success of this system is because it enables the user a remarkable similarity between the two worlds – real and virtual. The interaction with these two worlds is made through the same perceptual processes one interacts with within the real world. The sensation of "being there" is due to realism, isolation from the external physical environment, presentation, the inclusion of a large part of the senses (vision, touch and hearing), high resolution, and the consistency between stimuli and the system's response to the user's

movements. All these factors are responsible for the sensation of presence, which is, in turn, the principal active agent of the therapeutic process. (23)

PTSD is a field where VR can positively impact both the diagnosis and treatment. There are many barriers to medically assisted treatment due to the social stigma associated with mental disorders. In these situations, the logistics and economics associated with VR therapy encourage patients to adopt a VR-based treatment regimen. (24)

This study aims to determine the guidelines for designing a Virtual Reality - War Scenario program for Armed Forces veterans diagnosed with Post-Traumatic Stress Disorder.

2. Methods

2.1. Study 1

A systematic review was conducted to gather assumptions and requirements for designing a VRET programme for Portuguese armed forces veterans diagnosed with Post-Traumatic Stress Disorder. This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. (25) During February of 2021, searches were performed in the following electronic databases: B-on, PubMed, Clinical trials and Cochrane Library, and the following keywords were selected: ("Virtual Reality") AND ("Virtual Reality and PTSD") AND ("Veterans") AND ("Portuguese Colonial War") AND ("PTSD and VR and Veterans").

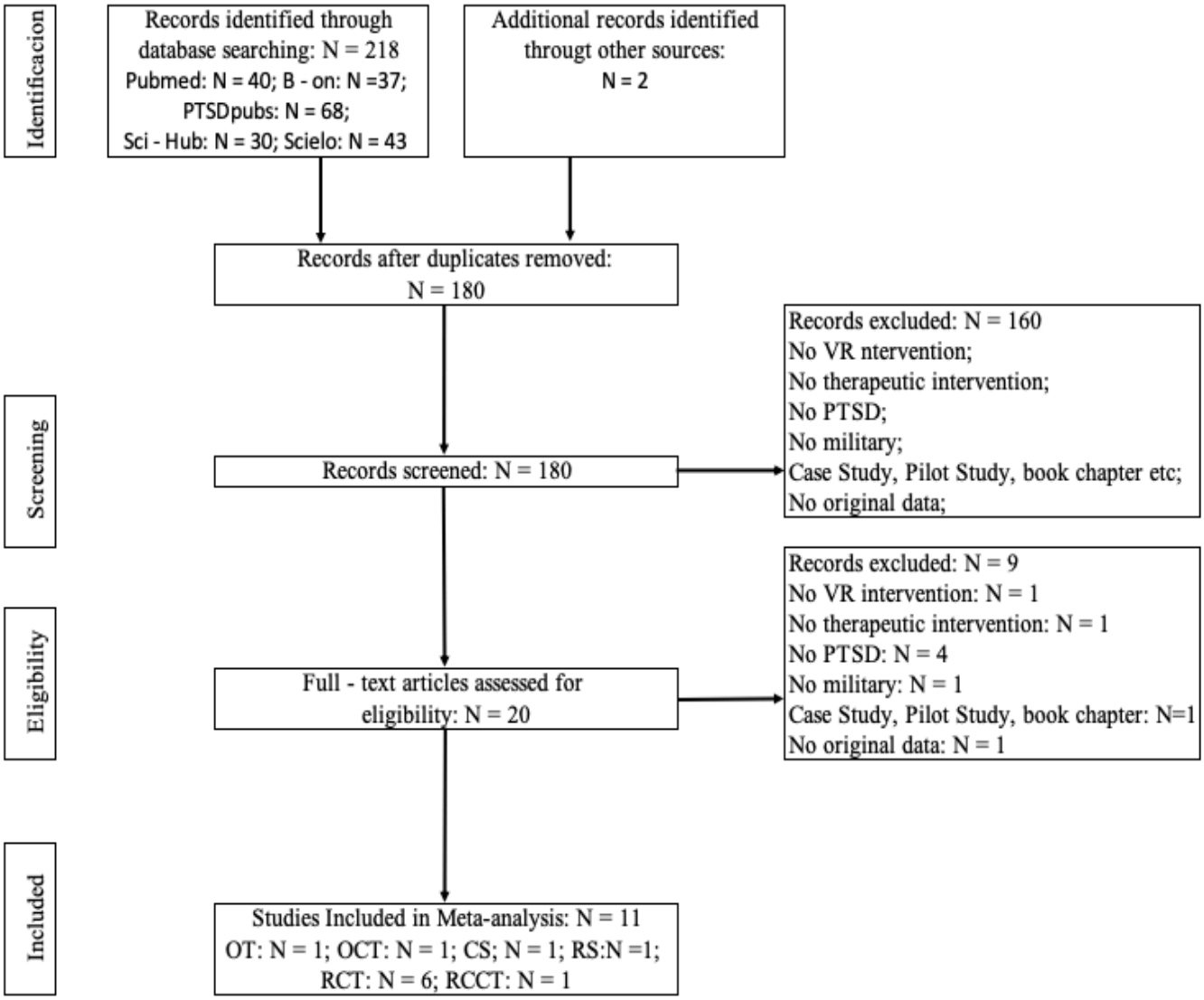
The search strategy was conducted without the year of publication limits in its study design, although it was restricted to search only the Portuguese and English languages. Database searches were supplemented by a bibliographic review of identified articles and consultation with subject matter experts.

Inclusion Criteria - 1. VRET was used as a therapy or as a supplement to evidence-based treatment to reduce PTSD symptoms; 2. The study focused on the efficacy of VRET to reduce PTSD symptoms; 3. PTSD symptoms were assessed with validated PTSD assessment instruments; self-reported or clinician-rated; 4. VRET minimally consisted of either an HMD that immersed a patient into a digital environment or a large projector screen that displayed the virtual environment.

Excluded Criteria - 1. Published in languages other than English or Portuguese; 2. Conference articles with superficial information, opinion articles, posters, chapters of books, theoretical articles that did not provide data from a case study, case report, or pilot study were excluded (Figure 1).

In the research, 218 studies were identified, and the first step was to remove duplicate titles. Then, the titles and abstracts were reviewed by two independent researchers. The complete article was evaluated in case of doubt about the study's inclusion only by its abstract. For studies that met the eligibility criteria, the full text was revised, and 11 papers were accepted for review, considering the eligibility criteria. A data-charting form was developed to determine which variables to extract, and Figure 1 outlines the study selection process. Bibliographic information, design, purpose, participants, measures, interventions, VR technology and key findings were collected and summarized in Table 1.

FIGURE 1 | PRISMA flowchart of screening, exclusion and inclusion criteria.



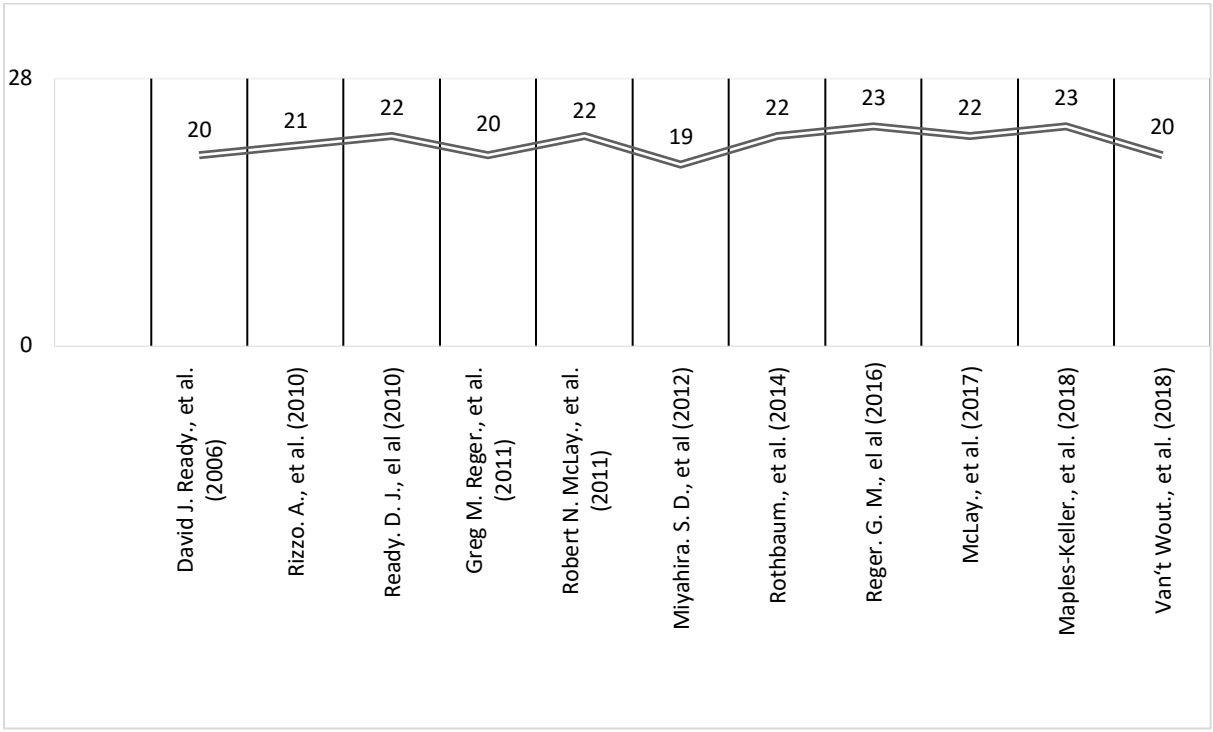
2.1.1. Quality assessment

Each selected article was assessed using a systematic quality assessment was performed for each article to determine the quality of reporting and the presence of methodological bias.

Studies were assessed for quality using the Downs and Black checklist. The checklist included four categories for evaluation: reporting, external validity, internal validity/bias, and internal validity/confounding. In addition, the methodological quality of all the included studies was assessed individually. (26) The score initially proposed for question 27, "Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?" underwent a small change. Instead of the five possible scores presented by the original authors, the results were altered to 0 or 1, based on whether the authors conducted a power analysis to detect a significant clinical effect (of at least 0.80, with alpha at 0.05) or not, with a score of 0 meaning "no" and one meaning "yes". Thus, the ratings of all 28 items were either yes (=1) or no/unable to determine (=0), except for item 5, in which the scores varied as yes (=2), partially (=1) and no (=0). Classification of the final scores fell into four categories: excellent (26–28), good (20–25), fair (15–19) and poor (14 and less).

According to the Downs and Black scores ten in eleven studies (N=10/11) 90.90% had a result of good (20-25), and only one (N=1/11) 9.09% had a result of fair (19 points) (Figure 2).

FIGURE 2 | Downs and Black (1998) – Checklist for assessment of the methodological quality



2.2. Study 2

The objective of the Focus Group was to develop, in a freeway, a dynamic on Virtual Reality (war scenarios), as well as its possible use in the treatment of Armed Forces veterans with war traumas (PTSD).

The eligible participants were Armed Forces veterans with war traumas (PTSD) involved in Colonial War or peace missions. Twenty-two participants were recruited by phone call. All participants were adequately and intelligibly informed about the study purpose and their role in it. The Focus Group took place at the Special Operations Troops Center (CTOE) Library and by videoconference via Zoom.

Before data collection, all participants signed consent forms and gave verbal permission to record the focus group session. Next, group members are asked to introduce themselves and to state what they know about VR. They are then asked to summarize their military histories. This introduction establishes the context of each person's participation.

2.2.1. Data collection

The focus group was conducted using semi-structured interview guidelines that included open questions about RV (war scenarios). Participants will be asked to discuss: 1) What do you know about VR; 2) how do they see VR as a therapeutic method; 3) VR Scenario characteristics and 4) VR Barriers.

Are examples of semi-structured interview questions: 1) How they would see, in general, the utilization of VR to help deal with PTSD?; 2) How they would see, in general, the utilization of VR to help deal with PTSD?; 3) What characteristics should the virtual environment have to unfold the stimulation?; 4) What narrative should it present? Where should you go? What is happening? When? With who?; 5) Important topics: narrative; context; characters.; 6) Should the scenario include different static levels?; 7) How should the instructions come up along the game? 8) How long should the game last?; 9) What precautions should we take?; 10) What are the advantages and disadvantages that are identified in its use?

The focus group was audio-recorded, and the information collected was encoded. In the next step, similar codes were grouped and organized into major themes and topics. The categories respected the criteria of relevance, homogeneity, objectivity and purpose.

The study was approved by the Ethics Committee of the School of Health, Polytechnic of Porto.(CE0064B).

3. Results

3.1. Study 1

Table 2 summarizes the study and treatment characteristics of the eleven articles included in this review. All selected papers were quantitative studies; the sample size was 641 subjects. The dropout rate was 160 subjects, in total 481 subjects remaining in the treatments. Patients were predominantly male (96.7%) and

female (3.3%). The mean age ranged from 18 to 62 years across studies. Studies included active-duty soldiers and veterans with combat-related PTSD. All selected studies for this review were carried out in the United States (N = 11/11; 100%).

In eight of the nine studies, the reduction in PTSD symptom severity was operationalized by the Clinician-Administered PTSD Scale. In one study, the reduction in PTSD symptom severity was operationalized by PCL-5 - PTSD checklist for DSM-5. Two studies (27,35) used the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM – IV) as the Instrument for PTSD diagnosis; the another two (28,30) used PTSD Checklist, Military Version (PCL – M); four (29,31,36,37) used Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM – 5); one study does not refer to the Instrument for PTSD diagnosis (32), and finally, the remaining two (33,34) used Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM – IV – TR).

The study design was a controlled trial, mostly randomized – six (31,33-37). The other studies used Retrospective Study (30), Randomized Controlled Clinical Trial (32), Open Trial (27), Open Clinical Trial (28), and finally Controlled study (29).

In all selected studies, the therapeutic framework was Prolonged Exposure. PE is an exposure therapy for PTSD that received the most empirical evidence for its efficacy. It is highly effective for patients with a wide variety of traumatic experiences. In a series of randomized controlled trials, PE demonstrated major treatment effects compared to waitlist (WL) control groups and similar results compared to other active treatments, such as stress inoculation training, cognitive processing therapy, eye movement desensitization and reprocessing. [38]

Most of the studies (45.45%) used the virtual Iraq/Afghanistan. The Iraq/Afghanistan VR system was developed by the Institute for Creative Technologies at the University of Southern California (Rizzo et al., 2009). This tool included a clinician's interface that allowed the therapist to customize the VR environment in real-time to match the patient's trauma memory characteristics. As the patient recounted their trauma memory during imaginal exposure, the therapist would fit the environment. (33-37)

These virtual environments included comprehensive prototype scenarios of combat-related PTSD experiences, such as riding in a Humvee through a desert. (7) The software has been designed so that users can be "teleported" to specific locations within the city, based on a determination as to which components of the environment most closely match the patient's needs relevant to their individual trauma-related experiences. (28)

The head-mounted displays – HMD used for 63.63 % of the studies was the eMagin z800. (28,30,33-37)

The sessions generally lasted between 30 and 120 minutes, and the average was 76.3 minutes per session. The number of sessions was between 3 and 20. Four studies included at-home in vivo exposure exercises (e.g. Listening to audio recordings of each VR exposure in the memory) (27–29,35).

Six out of eleven studies (54%) explored whether the efficacy of VRET may be increased through additional medication (30,21,33,34,36,37). Maples-Keller et al. (2018) (36) examined whether the administration of dexamethasone improved the efficacy of VRET compared to placebo treatment. Rothbaum and colleagues (2014) (33) analyzed to what extent D-cycloserine and alprazolam influenced the effectiveness of VRET, compared to a placebo group.

TABLE 1 | Descriptive characteristics = 11 included studies

References	Country	Instrument for PTSD diagnosis	Primary Outcome variable	Study design	Sample and trauma type	Participants	Dropout	Intervention	Time points of measurements and main results
Ready, David J., et al. (2006) (27)	USA	DSM-IV	CAPS	OT	Vietnam veterans with PTSD.	Total participants: N = 21 Male: 100%;	Total: N=6;	VRET	Measurements: Pre-, post-, and 3- and 6-month follow-up; Effect size (CAPS) All patients score on the 3- and 6-month follow-up assessments were below their pretreatment scores (range −15 to − 67%), p < .0001. Summary: All 14 patients showed reductions in PTSD symptoms compared to baseline by the 3-month follow-up assessment. These gains were maintained in 10 of the 11 patients who completed the 6-month follow-up assessment. In six of these patients, the CAPS scores continued to decline between the immediate post-treatment assessment and the 6-month assessment.
Rizzo. A., et al. (2010) (28)	USA	PCL-M	CAPS	OCT	Active duty soldiers.	Total participants: N = 20 Male: 90%; Female = 10%; Mean age = 28 years; Age range: 21–51 years;	Total: N=6;	VRET	Measurements: Pre-, post- Effect size (CAPS) Pre-/post-PCL-M scores decreased in a statistical and clinically meaningful fashion; mean (SD) values went from 54.4 (9.7) to 35.6 (17.4). Paired pre-/post-t-test analysis showed these differences to be significant (t = 5.99, df = 19, P < 0.001). Summary: 80% of the treatment completers in this VRET sample showed both statistically and clinically meaningful reductions in PTSD, anxiety and depression symptoms, and anecdotal evidence from patient reports suggested that they saw improvements in their everyday life situations. These improvements were also maintained at 3-month post-treatment follow-up.
Ready. D. J., el al (2010) (29)	USA	DSM-5	CAPS	CS	Vietnam veterans with PTSD.	Total participants: N = 11 VRET: N = 6 Male: 100 %; Mean age = 57; Age range: 53–61 years; PCT: N = 5 Male: 100% Mean age = 58; Age range: 55 - 62 years;	Total: N=2; VRET: N = 1; PCT: N = 1;	VRET vs PCT	Measurements: Pre-, post-, and 6-month follow-up Effect size (CAPS) Summary: VR - 31.8 (SD1/439.1) from pre- to post- and of 25.0 (SD 1/4 28.1) from pre- to follow-up, Cohen`s of 0.28 and 0.56; BDI - 5.0 (SD 1/4 8.7) from pre- to post- and of 2.3 (SD 1/4 7.8) from pre- to follow-up. PCT - 23.0 (SD1/421.9) from pre- to post- and of 13.0 (SD 1/4 11.3) from pre- to follow-up; Cohen of 0.0 and - 0.24; BDI - of 5.0 (SD1/47.5) from pre- to post- and of 4.3 (SD 1/4 8.8) from pre- to follow-up. Combining groups - CAPS scores from pre- to post- (t 1/4 2.70, p < 0.05) and from pre- to 6-month follow-up (t1/42.58, p<0.05). No statistically significant improvement in CAPS or BDI scores when individual treatment conditions were isolated. Summary: possible value of VRE while pointing out that the primary difficulty with further investigation of this treatment model with older veterans is participant recruitment.

TABLE 1 | Descriptive characteristics = 11 included studies – Continued

References	Country	Instrument for PTSD diagnosis	Primary Outcome variable	Study design	Sample and trauma type	Participants	Dropout	Intervention	Time points of measurements and main results
Reger, Greg M., et al. (2011) (30)	USA	PCL-M	CAPS	RS	Active duty soldiers.	Total participants: N = 32 Male: 96%; Mean age: 28.8, Gender: n.r.; 75% were diagnosed with PTSD (n = 18);	Total: N= 8;	VRET	Measurements: Pre-, post- Effect size (CAPS); Pretreatment PCL-M (M = 60.92; SD = 11.03), patients receiving VRE reported a statistically significant drop in PTSD symptoms (M = 47.08; SD = 12.70), t (23) = 6.53, p < .001, d = 1.17; At post-treatment, differences on the PCL-M were no longer significant between those with PTSD (M = 49.72; SD = 13.20). Summary: Patients receiving an average of seven sessions of VRE reported statistically and clinically significant reductions in self-reported symptoms of PTSD.
McLay, Robert N., et al. (2011) (31)	USA	DSM-5	CAPS	RCT	Active Duty military personnel with combat-related PTSD.	Total participants: N = 20, VR-GET: N=10 Male: 90% Mean age: 28.8; Gender: 22-43; TAU: N=10 Male: 100%; Mean age: 28; Gender: 21-45;	VR-GET: N= n.r; TAU: N = n.r;	VR-GET vs TAU	Measurements: Pre-, post-, and 10-week follow-up; Effect size (CAPS); VR-GET: N=10, (70%) of these showed a 30% or greater improvement in the CAPS. TAU: N=10, One (11.1%) of the 9 returning participants receiving TAU showed >30% improvement on the CAPS. Chi-square for the treatment response comparison between VR-GET and TAU was 6.74, p < 0.01. With Yates correction w2 1/4 4.54, p < 0.05, relative risk was 3.21, with 95 % confidence interval 1.18 to 8.72. Pre-vs. post-treatment, p < 0.001), but not group (p > 0.05). There was a significant time-by-group interaction (p<0.05). There was no significant difference between VR-GET and TAU mean CAPS score before or after treatment, but there was a significant difference in the mean CAPS change score over the course of treatment (35.4 vs. 9.4, p < 0.05). Summary: 70% of participants who received VR-GET showed a clinically significant (>30%) improvement in their PTSD symptoms after 10 weeks of treatment. This was a significantly (p<0.05) greater percentage than the 12.5% of participants who showed clinically significant responses in usual treatment.
Miyahira. S. D., et al (2012) (32)	USA	n.r.	CAPS	RCCT	Active duty service members with PTSD symptoms who participated in military operations in Iraq or Afghanistan	Total participants: N = 99 Male: N =94 Female: N = 5 VRE=12 MA=10	Total: N = 77	VRE vs MA	Measurements: Pre-, post- Effect size (CAPS); Significant decrease over time on the CAPS Criterion C (avoidance/numbing symptoms) in the VRE group (F (1,20) = 6.03, p=.02); The VRE group scored significantly lower on the CAPS Criterion C compared to the MA group at post-procedures (F (1, 20) = 8.705, p = 0.008). Summary: VR exposure may be effective in reducing some PTSD symptoms in active duty service members returning from combat theaters.

TABLE 1 | Descriptive characteristics = 11 included studies – Continued

References	Country	Instrument for PTSD diagnosis	Primary Outcome variable	Study design	Sample and trauma type	Participants	Dropout	Intervention	Time points of measurements and main results
Rothbaum., et al. (2014) (33)	USA	DSM-IV-TR	CAPS	RCT	War veterans with Iraq and Afghanistan deployment Combat-related PTSD symptoms.	Total participants: N = 156; Males = 94% Mean age: 35.1; Gender: 148; VR treatment group (VRET with DCS): n = 53; Males = 92% Mean age: 34.9; Gender: 49; Active control group (VRET with Alprazolam): n = 50; Males = 98%; Mean age: 36.2; Gender: 49 Control group (VRET with placebo): n = 53; Males = 94%; Mean age: 34.3; Gender: 50;	Total: N = 59 (37%); VR treatment group (VRET with DCS) N = 25 (47%); Active control group (VRET with Alprazolam): N= 15 (30%); Control group (VRET with placebo) N = 19 (35%);	VRET with DCS vs. VRET with Alprazolam vs. VRET with Placebo	Measurements: Pre, post, 3, 6, and 12 month-follow-up; Effect size: n.r. and n.a.# Summary: All groups decreased significantly on the CAPS. The effect maintained over 12 months-follow-up. At post-treatment there was no significant difference between D-cycloserin and placebo group on the CAPS. However, there was a significant difference favoring placebo over alprazolam regarding the CAPS at post-treatment.
Reger. G. M., et al (2016) (34)	USA	DSM–IV-TR	CAPS	RCT	Active-duty soldiers.	Total participants: N = 162; WL: N= 53; Males = 98.15%; Mean age: 30.39 (6.45); PL: N= 51; Males = 94.44%; Mean age:30.89 (7.09); VR: N =52; Males = 96.30%; Mean age: 29.52 (6.47);	Total: N = 6	VRE vs PE	Measurements: Pre, midtreatment, post, 12-week and 26-week; Effect size (CAPS); VRE - Pre, 80.44 (16.23); 26-week, 53.50 (28.07); PE - Pre, 78.28 (16.35); 26-week, 38.33 (28.49); WL - Pre, 78.89 (16.87); 26-week, n.r.; Summary: Results extend previous evidence supporting the efficacy of PE to active-duty military personnel and raise important questions for future research on VRE.
McLay., et al. (2017) (35)	USA	DSM-IV	CAPS	RCT	Active duty military members with past Iraq and Afghanistan deployment Combat-related PTSD symptoms.	Total participants: N = 81; Males = 96.3%; Mean age: 32.5; Gender: 78; VR treatment group (VRET with immersive technology): n = 43; Males = 93% Mean age: 33; Gender: 40; Active control group (VRET with non-immersive technology): n = 38; Males =100%; Mean age: 32; Gender: 38;	Total: N = 7 (8%); VR treatment group (VRET with immersive technology): N = 7 (16%); Active control group (VRET with non-immersive technology): N = 0 (0%);	VRET with immersive technology vs. VRET with non-immersive technology	Measurements: Pre, post, and 3 month-follow-up Effect size (CAPS): Hedges' gpost = -0.33# (favoring VRET with non-immersive technology) Hedges' g3month = 0.15# (favoring VRET with immersive technology) Summary: Significant decrease on the CAPS maintained over 3 month-follow-up. No significant differences between groups were found.

TABLE 1 | Descriptive characteristics = 11 included studies – Continued

References	Country	Instrument for PTSD diagnosis	Primary Outcome variable	Study design	Sample and trauma type	Participants	Dropout	Intervention	Time points of measurements and main results
Maples-Keller., et al. (2018) (36)	USA	DSM-5	CAPS	RCT	War veterans and active duty personnel with past Iraq and Afghanistan deployment Combat-related PTSD symptoms.	Total participants: N = 27; Males = 100%; Mean age: 35.4, Gender: 27 VR treatment group (VRET with dexamethasone): N= 13; Males = 100%; Mean age: n.r.; Gender: 13; Active control group (VRET with placebo): N = 14; Males = 100%; Mean age: n.r.; Gender: 14;	Total = 3 (12%), VR treatment group (VRET with dexamethasone): N= 0 (0%); Active control group (VRET with placebo): N= 3 (25%);	VRET with dexamethasone vs. VRET with placebo	Measurements: Pre and post Effect size (CAPS): Combined sample Cohen's dpre-post = n.r. Summary: Significant decrease on the CAPS for post-treatment but no significant differences between groups.
Van't Wout., et al. (2018) (37)	USA	DSM-5	PCL-5	RCT	War veterans with Iraq and Afghanistan deployment Combat-related PTSD symptoms.	Total participants: N = 12; Males =100%; Mean age: 40.5; Gender: 12 VR treatment group (VRET with tDCS): N = n.r.; Mean age: n.r.; Gender: n.r.; Active control group (VRET with sham tDCS): N = n.r.; Mean age: n.r.; Gender: n.r.;	Total = n.r.; VR treatment group (VRET with tDCS) N= n.r.; Active control group (VRET with sham tDCS) N = n.r.;	VRET with tDCS vs. VRET with sham tDCS	Measurements: Pre, post, and 1 month-follow-up Effect size (PCL-5): Hedges' g_{post} = 0.20# (favoring VRET with tDCS) Cohen's d1month = 0.37 Summary: Both groups demonstrated significant reductions in PCL scores. There were no significant differences between groups at post time measurement, but VRET with tDCS were superior to VRET sham tDCS at 1 month-follow-up.

'SA, United States of America; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders 4th Edition Text Revision; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th Edition; DSM-5, Diagnostic and Statistical Manual of Mental Disorders 5th Edition; APS, clinician-administered PTSD scale, measured via CAPS total sum score; PCL-5, PTSD checklist for DSM-5, measured via PCL-5 total sum score; RCT, randomized controlled trial; PTSD, post-traumatic stress disorder; MST, military sexual trauma; n.a., not applicable; 'R, virtual reality; VRET, virtual reality exposure therapy; TMT, trauma management therapy; n.r., not reported; DCS, D-cycloserine; tDCS, transcranial direct current stimulation; PE, prolonged exposure; Hedges' g# , a Hedges'g marked by "#" was recalculated. For the ecalculation, we used means, standard deviations and sample sizes for the respective studies and followed the procedure by Hedges and Olkin (2014); Pre, pre-treatment assessment; Post, post-treatment assessment; n.a.#, not applicable, because these studies did not eported standard deviations. Instead they reported mean values and 95% confidence intervals; VR-GET, Virtual Reality-graded exposure therapy; TAU, treatment as usual; OT, Open trial; VRE, Virtual Reality Exposure; RS, retrospective study; PCL-M, PTSD Checklist, Military 'ersion; OCT, open clinical trial; PDS, PTSD Diagnostic Scale; BDI-II, Beck Depression Inventory II; QOLI, Quality of Life Inventory; TRGI, Trauma Related Guilt Inventory; MA, Minimal attention; RCCT, Randomized controlled clinical trial; WL, Waitlist control; CS, Controlled study; 'CT, Present-centered therapy.

TABLE 2 | Results of the qualitative analysis for each study.

References	Therapeutic framework	Period of time	Number of sessions	Medication	Homework	Hardware	Software
David J. Ready et al. (2006) (27)	PE	Two 90-min;	8 to 20;	n.r.;	Yes – Breathing exercise for stress management and was asked to practice this exercise daily;	n.r.;	Virtual Vietnam
Rizzo, A et al. (2010) (28)	PE	2× weekly, 90–120 min sessions over 5 weeks;	10;	n.r.;	Yes – First item in a hierarchical list about a traumatic event and listen to the audiotape of their exposure narrative from the most recent session;	HMD – eMagin z800;	Virtual Iraq
Ready, D. J., el al (2010) (29)	PE	n.r.;	10;	n.r.;	n.r.;	n.r.;	n.r.;
Greg M. Reger et al. (2011) (30)	PE	90-minute;	3 to 12;	Yes – 77% N = 16; Antidepressants – N = 12; Prazosin – N = 8; Aleep aids – N = 7; Quetiapine – N= 1; Lamotrigine – N = 1; Hydroxyzine pamoate – N = 1	Yes – Listening to audio recordings of each VR exposure to the memory;	HMD – eMagin z800;	Virtual Iraq
Robert N. McLay et al. (2011) (31)	PE	VR-GET – 1x a week for up to 10 weeks; TAU – 10 weeks;	VR-GET – 10; TAU – 14	Yes – psychotropic medications;	n.r.;	n.r.;	n.r.;
Miyahira, S. D., et al (2012) (32)	PE	2 sessions per week for 5 weeks;	10;	n.r.;	n.r.;	n.r.;	n.r.;
Rothbaum et al. (2014) (33)	PE	90-min; 45-min;	6; 5;	Yes – D-cycloserine (50 mg); Alprazolam (0.25 mg); The placebo medication 30 min before exposure;	n.r.;	HMD – eMagin z800	Virtual Iraq/Afghanistan;
Reger, G. M., et al (2016) (34)	PE	90–120 min;	10;	Yes – n.r.;	No – n.r.;	HMD – eMagin z800	Virtual Iraq/Afghanistan;
McLay et al. (2017) (35)	PE	90-min; 30-45 min;	8 to 12; 5 to 9;	n.r.;	Yes – Confronting real life stresses *in vivo*;	HMD – eMagin z800	Virtual Iraq/Afghanistan;
Maples-Keller et al. (2018) (36)	PE	90-min of 7 to 12 weeks; 30-45 min;	7 to 12; 6 to 11;	Yes – Dexamethasone (0.5 mg) or placebo the night before virtual exposure;	n.r.;	HMD – eMagin z800	Virtual Iraq/Afghanistan;
Van't Wout et al. (2018) (37)	PE	90-min of 2 weeks; 30-45 min;	6; 6;	Yes – n.r.;	n.r.;	HMD – eMagin z800	Virtual Iraq/Afghanistan;

E, Prolonged exposure; Min, Minute; n.r., not reported.

3.2. Study 2

The focus groups were moderated by one of the authors and were conducted for about 90 minutes. The debate was serene, flowed naturally, and the intervention of the re-searcher/moderator was hardly necessary because the points that needed to be addressed were defined from the beginning.

Content analysis emerged on three main themes: (1) Importance of VR in PTSD, (2) VR software, (3) VR Barriers. (See Table 3).

VR Potential – None of the participants knew about Virtual Reality, much less it could be used as a therapeutic tool in PTSD. After a brief explanation about VR, how it can be used, and its significant advantages, all participants agreed that it would be innovative and pertinent to technology combined with therapy. One of the former combatants said, "*the technology finally came to us*" which shows the receptivity of this group to this therapy.

VR software –The interdisciplinary nature of VR and its evolution allows the user's immersion, navigation and interaction with a given platform or scenario generated by a computer to be explored by various human senses and feelings, allowing the user to exist in three dimensions: visual, sensory and kinesthetic (39). This line of thought guided the sessions to understand the relevant points in these three dimensions and whether these three dimensions should be considered when creating a War scenario for Armed Forces veterans with PTSD.

All participants agreed that hearing, touch, and smell stimuli should be present in a War scenario. The smell of rain, wet earth is impregnated in their memories to this day, and after so many years, it is the smell they remember most. "*The smell of heavy rain*"; "*The smell of the first rains and the earth*". The sense of smell allows a closer approximation with reality in possible risk training sessions or psychological intervention on traumatic events. (39)

Immersion was another fundamental factor and idea present in the Focus Group sessions. It is crucial to have the feeling of presence to create the idea of being in another place, a place full of memories, which will make the feeling of involvement. The in-volvement, in turn, is linked to the degree of personal motivation in a particular task or activity.

For the sense of presence to be guaranteed, it must ensure sensory fidelity, which corresponds to creating an environment with the highest possible degree of "realism". However, making sense of presence is not limited to "showing" and "recreating" scenarios. It also implies interactivity and a psychological component.

(40) "*The scenario should be dynamic and realistic", "I want to feel what I felt before, look and see my memories, my pain*".

The storyline, the quality of the narrative, and its elements are fundamental to the realism that this scenario must-have. There is a military language, clothing, weapons, vehicles, fauna and flora that will have to be present so that the illusion of presence is complete on four levels: spatial (feeling you are in a particular place); corporal (feeling you have a body); physical (being able to interact with the elements of the scenario) and social (being able to communicate with the characters in the environment). (41) "The bombing drove away the fauna and flora", "The enemy was also the mosquitoes", "There was no helmet, there were many mines", "We acted in groups", "I slept two years in the bush under a cloth tent", "There were no civilians, anyone who appeared after you left the barracks was considered an enemy".

To provide a more immersive experience, it must be possible for the individual to interact and modify the virtual environment in which he is sensorial inserted, considering his emotional state. This change in the environment should be linked to the computer's ability to detect the user inputs and instantly modify the virtual world according to its actions. This reactive capacity of the computer allows the scenes to change in response to user commands. (36) "We should have instruction before starting the immersion", "The evolution in the scenario should be automatic", "15 to 20 minutes is enough to experience the scenario".

It is essential that the environment created is as faithful as possible, which implies that a lot of detail matches the sensory world. These aspects are fundamental since the user takes several pieces of information from the scenario to locate himself spatially.

VR Barriers – The only barrier or concern that veterans had was that they were not prepared to "enter" a war scenario again. Before they were physically and psychologically prepared to fight the enemy, they no longer had any training with these skills. "With time, how am I going to react? Before, I was prepared, but now I'm not."

TABLE 3 | Results of Study 2 - Focus Group

VR Potencial	**VR software**	**VR Barriers**
Motivation; Technology combined with traditional therapy.	Dynamic scenario; Multisensory; Realistic; Immersive; Envelopment; Stimulate the imagination;.	Not prepared to "enter" a war scenario again.

4. Discussion

4.1. Summary of Findings

This study explores the effectiveness of VRET for PTSD in veterans and the most appropriate requirements for their implementation. According to the systematic literature search and review, the Virtual Reality in the Treatment of Post-Traumatic Stress Disorder in Former Armed Forces Combatants seems beneficial.

The systematic review revealed that all the VRET protocols studied showed a positive impact on a range of symptoms. All treatment gains were maintained at three, six- and 12-month follow-up. (27–37)

Most of the studies on VRET included 3–20 virtual exposure sessions, lasting 30–120 min. These studies were based on the Emotional Processing Theory (EPT). In this theory, fear is represented in memory as structures made up of associated stimulus, response, and meaning elements designed as a program to avoid or escape danger. (42) Traumatic events modify the basic beliefs of an individual since negative beliefs about the world, oneself, and others increase. (42,43)

Since the key in emotion processing theory (PTSD) is to expose and modify its unique fear structure, discharged soldiers can control some of their destructive behaviors resulting from PTSD in a safe environment and learn how to solve these situations. (44) The VR enables the patient to explore emotions while decreasing the sense of threat. It is essential to monitor anxiety levels through advanced systems and process the patient's sensations and feelings. Any alarm should indicate to the therapist how to manage the intensity of the simulations not to cause worse harm to the patient. (14) One of the advantages of VR is to allow the therapist to control moment by moment, documenting and measuring the patient's responses to stimuli. (45)

The development of this VR programme could involve, graphic models, and narrative. (14) All these factors were considered relevant in the Focus Group Sessions, the narrative being one of the essential points in creating a realistic War scenario for the Armed Forces veterans. The Focus Group also highlighted that the specific content should be discussed in a group, then worked on with the VR resources before starting the program and not at the end. Furthermore, it is essential that the Ex-combatants contact the VR to permit habit and that the adverse effects can be supplemented from the beginning. Another crucial factor is the individual's initial evaluation

before exposing him to the VR, to guarantee that the security conditions are reunited for their participation.

The VRET protocols varied according to whether medication, at-home in vivo exposure exercises, number of sessions and period of time. Continuous monitoring is also referred to as essential. It avoids demotivation of the participants, which can cause them to give up. This monitoring may be passed on as homework (Table 2). (27,28,30,34)

In terms of the human interface, the results showed that HMDs were used in seven studies. Detailed analyses revealed that 75% of the HMDs were released in 2005–2006, and the remaining 25% were released in 2012–2013. Therefore, it is necessary to deepen the effectiveness of this technology for a better understanding of its effects. (46) However, VR and its application also have limitations. The immersive nature of HMDs creates a strong presence illusion, where users perceive virtual environments (VEs) as real and not mediated through technology. The major practical issue with HMDs is that users commonly report adverse physical reactions, including headaches, nausea, dizziness, and eye strain when using them. Collectively, these symptoms represent a condition termed simulator sickness, which reportedly affects up to 80 percent of HMDs users. (47,48)

Therefore, a solution that addresses discomfort experiences during a user's first HMD exposure is essential to the continued growth and adoption of VR. This visual discomfort of VR can lead to treatment abandonment. Therefore, besides studying the efficacy of VRET, it is also crucial to investigate the safety of the treatment.

Several reviews did not specify the hardware (27,29,31,32) or software (29–32) used in included studies. Although this could be a limitation of systematic reviews, all data must be provided to understand the study better.

The software also imposes limitations (which we intend to address with the requirements survey conducted in the Focus Group). The software is often restricted to protocols created that will hinder an adequate virtual environment for the specific needs of each patient or group. Because of the pre-programmed scenarios, creating a virtual trauma-related environment that completely matches the patient's recounting is impossible. Therefore, breaks in the sense of spatial or social presence and plausibility may occur. (49)

The lack of standardized protocols is also a limitation of this therapy, which indicates the need for more research and investigation for its constitution. The publication of protocols is of vital importance to reduce costs and time that can be shared by the scientific community, in which the strengths and weaknesses are listed to avoid the elaboration of treatment and scenarios by trial and error. [49]

Pre-programmed virtual scenarios were used in VRET (27,28,30,33–37), so it may not be possible to create a trauma-related virtual environment that fully matches the patient's narrative, which may lead to incongruity. Therefore, breaks in the sense of presence, as well as in spatial or social plausibility, can occur. (50) The choice of hardware and software depends on the type of virtual trauma intervention; the advantages and disadvantages influence the sense of presence that is supposed to significantly impact VR scenarios' success.

The results revealed that neither spatial nor social presence was assessed in any of the 11 studies. All interventions with VR scenarios are based on the assumption that the sense of presence is an essential prerequisite. This aspect illustrates the need for effective research to examine whether spatial presence is a crucial mechanism for shaping the efficacy of virtual trauma interventions. (51)

There is also no empirical evidence in any 11 studies on whether virtual trauma intervention is particularly effective for PTSD patients with imagination difficulties. Thus, future research is required to establish whether virtual trauma interventions are particularly effective for PTSD patients with imagination difficulties.

5. Conclusion

The results of this systematic review suggest the potential efficacy of VRET in the treatment of PTSD. VRET can be particularly useful in treating PTSD resistant to traditional exposure. It provides the ability to conduct extinction training/exposures for stimuli that may be too expensive or not feasible to implement in vivo, such as virtual combat situations. New VRET programs developments must consider as requirements the sense of presence (spatial and/or social); dynamic scenario; realistic; multisensory and stimulate the imagination. In this co-creation process, researchers must involve end-users and access all research developed on the subject to personalise the intervention and avoid future mistakes.

More research in this area should carry out to obtain more robust scientific evidence.

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