Journal of Affective Disorders 257 (2019) 698–709

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review article

The efficacy of virtual reality exposure therapy for PTSD symptoms: A systematic review and meta-analysis

Deng Wenrui[a], Hu Die[a], Xu Sheng[a], Liu Xiaoyu[a], Zhao Jingwen[a], Chen Qian[a], Liu Jiayuan[b], Zhang Zheng[b], Jiang Wenxiu[c], Ma Lijun[d], Hong Xinyi[e], Cheng Shengrong[e], Liu Boya[e], Li Xiaoming[a,*]

[a] Department of Medical Psychology, Chaohu Clinical Medical College, Anhui Medical University, Hefei, Anhui 230032, China
[b] Department of Medical Anesthesia, the First Clinical Medical College of Anhui Medical University, Hefei, Anhui 230032, China
[c] Department of Stomatology, Stomatology College of Anhui Medical University, Hefei, Anhui 230032, China
[d] Department of Psychology, School of Education, Anqing Normal University, Anqing, Anhui 246133, China
[e] Department of Clinical Medical, the First Clinical Medical College, Anhui Medical University, Hefei, Anhui 230032, China

A B S T R A C T

Background: Virtual reality exposure therapy (VRET) for PTSD is an emerging treatment of remarkable promise, but its efficacy and safety are still unclear. Our aim was to investigate the efficacy of VRET for individuals with PTSD, and to identify the potential moderating variables associated with interventions.
Methods: Literature search was conducted via PubMed, Embase, Web of Science, Cochrane Library, PsycInfo, Science Direct, and EBSCO. We identified 18 studies on PTSD including 13 randomized controlled trials (RCTs; 654 participants) and 5 single-group trials (60 participants).
Results: The main effects analysis showed a moderate effect size ($g = 0.327$, 95% CI: 0.105–0.550, $p < 0.01$) for VRET compared to control conditions on PTSD symptoms. Subgroup analysis revealed that the effects of VRET were larger when compared to inactive groups ($g = 0.567$) than active control groups ($g = 0.017$). This finding was in agreement with depressive symptoms. A dose–response relationship existed with more VRET sessions showing larger effects. There was a long-range effect of VRET on PTSD symptoms indicating a sustained decrease in PTSD symptoms at 3-month follow-up ($g = 0.697$) and 6-month follow-up ($g = 0.848$). The single-group trials analysis revealed that the VRET intervention had a significant effect on PTSD.
Limitations: Many of the combat-related PTSD subjects resulted in uncertainty regarding meta-analytical estimates and subsequent conclusions.
Conclusions: These findings demonstrated that VRET could produce significant PTSD symptoms reduction and supported its application in treating PTSD.

1. Introduction

Posttraumatic stress disorder (PTSD) is a prevalent mental health problem worldwide. The recent World Health Organization World Mental Health Surveys estimate that the lifetime prevalence of PTSD was 3.9% across nations and 5.6% among the trauma exposed (Koenen et al., 2017). Especially those who exposed to military combat, are at a higher risk of developing PTSD and it has been reported that up to 18% of Operation Iraqi Freedom veterans have experienced PTSD (Rothbaum et al., 2010). PTSD is a chronic and disabling psychiatric disorder that may develop following exposure to a traumatic event (e.g., combat, death, threatened death, serious injury, sexual violence) (Jorge, 2015; Kessler et al., 2012). The DSM-5 identifies the types of events capable of producing PTSD, which are either directly experienced, witnessed, experienced by a close family member or friend, or experienced through actual or threatened death, serious injury or sexual violence, repeated or extreme exposure to aversive details of the traumatic event, and categorizes PTSD symptoms as: re-experiencing, avoidance, negative alterations in mood and cognition, and alterations in arousal and reactivity (APA, 2013). Individuals suffering from PTSD endure and exaggerate negative beliefs about oneself, others or the world, and cling to the cause or consequences of the event(s) combined with significant distress, anxiety and functional impairment, as well as social ramifications.

Fortunately, a range of interventions, both pharmacological and psychological, exist for ameliorating PTSD and related symptoms (Cukor et al., 2009). In addition, trauma-focused cognitive-behavioral treatments (CBT) are psychotherapy based on principles of conditioning and learning. For example, exposure therapy is regarded as the first-line treatment for PTSD given its well-documented clinical efficacy (Foa et al., 1999, 2003; Powers et al., 2010). Other trauma-focused interventions, based on CBT including prolonged exposure (Foa et al., 1999), cognitive processing therapy (CPT) (Monson et al., 2006) and eye movement desensitization and reprocessing (EMDR) (Bisson et al., 2007), have been endorsed to be effective. Besides, evidence suggests that non-trauma focused interventions (e.g., present-centered therapy,

* Corresponding author.
E-mail address: psyxiaoming@126.com (X. Li).

https://doi.org/10.1016/j.jad.2019.07.086
Received 2 April 2019; Received in revised form 27 July 2019; Accepted 29 July 2019
Available online 30 July 2019

PCT) are also effective to treat PTSD (Foa et al., 2018).

However, despite abundance of evidence pointing to the effectiveness, there is a major disadvantage of traditional interventions. The subjects reported that it is difficult to fully immerse in the traumatic scene and the treatment of exposure therapy (Cadth, 2014) in the traditional interventions, which cause high dropout rates (up to 48%) (Cottraux et al., 2008; McDonagh et al., 2005). Thus, PTSD remains a difficult disorder to treat and calls for the innovation and dissemination of alternative or augmented treatments.

It is worth noting that exposure therapy based on virtual reality (VR) technology has a potential efficacy in the treatment of PTSD for different types of trauma (Bloch et al., 2013) and it can make up for the shortcomings of traditional therapy. VR, using head-mounted computer simulations of sights, sounds, vibrations and smells tailored to the patient's individual trauma, integrates real time computer graphics with multiple sensory cues in order to create an evocative environment that may augment a patient's imaginative exposure with visual, auditory, olfactory, and haptic computer-generated experiences (Gerardi et al., 2010, 2008). Therefore, virtual reality exposure therapy (VRET) offers a promising technological adjunct to traditional exposure for PTSD treatment. Imaginal exposure, for example, requires patients to repeatedly narrate their trauma-related experiences with their eyes closed to facilitate their imaginative engagement. However, the inherent avoidance of traumatic memory may render an engagement in imaginal exposure impossible for some patients. One fundamental principle of VRET is the ability of trauma-related, multi-sensory stimulation, therefore it can increase emotional engagement. A meta-analysis using 46 studies with a combined sample size of 1,057 anxiety participants yielded an estimated dropout rate of 16.0% from VRET indicates that attrition rate of VRET is lower than the attrition rates of CBT and traditional therapy (Benbow and Anderson, 2019). What's more, VRET allows for the standardization of the duration and type of exposure for all patients in order to reach greater methodological rigor in clinical studies (Rothbaum, 2009). In this sense, VR has been used as a tool for exposure, saving time and money in the process of exposure, and has achieved positive results in the treatment of various anxiety disorders including specific phobias, acrophobia, social phobia, generalized anxiety, disorders panic disorder and PTSD (Botella et al., 1998; Carlin et al., 1997; Rothbaum and Hodges, 1999; Wolitzky-Taylor et al., 2008).

Studies evaluating the efficacy of VRET relative to existing standards of care for PTSD symptoms have involved varying methodologies, time-frames, and samples, but the results are mixed. For instance, some studies suggest that VRET significantly reduce the severity of post traumatic symptoms compared to other interventions (Difede et al., 2007; Gamito et al., 2010; McLay et al., 2011; Miyahira et al., 2012; Ready et al., 2010; Roy et al., 2010), while other studies suggest that the efficacy of VRET is no better than some traditional treatments (McLay et al., 2017; Reger et al., 2016). Yet other studies suggest the efficacy of VRET was no better than some traditional treatments when the treatment ended, but in the later follow-up, the VRET group shows better relief than other interventions in post-traumatic symptoms (McLay et al., 2011; Ready et al., 2010).

A recent systematic review outlines literatures about VRET in treatment of PTSD (Goncalves et al., 2012). However, it did not report overall effect sizes and the influence of the major moderators in PTSD due to be a systematic review. In addition, there is increasing evidence indicating the efficacy of VRET in PTSD and depressive symptoms, however the review did not include these studies (Beidel et al., 2017; Difede et al., 2014; McLay et al., 2017; Reger et al., 2016; Rothbaum et al., 2014). Consequently, the efficacy and safety of VRET for PTSD and whether there is different efficacy between VRET and other interventions are unclear. To date no study has used meta-analytical techniques to pool the existing evidence to evaluate the efficacy of VRET on PTSD. Moreover, one meta-analysis of VRET in anxiety disorders finds that there exists a trend for a dose–response relationship which means the more treatment sessions, the larger effect sizes (Opriş et al., 2012). However, whether there also exists a dose–response relationship on VRET in PTSD is still unknown. Similarly, whether there is a long-term therapeutic effect during follow-up is unknown. More recently, several single-group pre- and post-test trials examined the effectiveness of VRET in patients with PTSD (Beck et al., 2007; Ready et al., 2006; Rizzo et al., 2010; Wood et al., 2011; Zinzow et al., 2017), however no dedicated systematic review and meta-analysis has assessed the efficacy of VRET for PTSD symptoms in single-group trials. While there is evidence that estimates from high-quality single-group trials can overcome the lack of prospective randomized evidence and that the results may be similar to randomized controlled trials (RCTs), and that the collection of high-quality single-group trials may be as accurate as the summary RCTs (Hosono et al., 2006; Yakoub et al., 2009; MacLehose et al., 2000).

Given these limitations and inconsistence in the literature, we conducted this comprehensive systematic review and meta-analysis to investigate the role of VRET as a therapy for patients with PTSD.

2. Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (PRISMA) (Liberati et al., 2009) and was organized adhering to previously recommended guidelines for transparent and comprehensive reporting of methodology and results. The PROSPERO ID of this Systematic Review's protocol is CRD420180082494.

2.1. Search strategy

We conducted an electronic search of the following databases: PubMed, Embase, Web of Science, Cochrane Central Register of Controlled Trials, PsycInfo, Science Direct, and MEDLINE Complete database of EBSCO from inception to June 9, 2019 (full search strings are provided in Supplemental Material). For additional references to potentially relevant studies, we checked reference lists of relevant studies and reviews. Furthermore, we also asked key researchers in the field whether they knew of unpublished trials.

2.2. Eligibility criteria

Eligible studies were randomized controlled trials (RCTs) and single-group trials included participants with a primary diagnosis of PTSD, examining the effects of exposure interventions delivered via virtual reality devices with outcome measures intended to assess PTSD or depressive symptoms. The control groups were received at least one non-VRET group, including cognitive behavior therapy (CBT), prolong exposure (PE), attention controls, present-centered group therapy (PCGT), treatment as usual (TAU), waiting list. Then, control groups were furthermore specified as active or inactive. “Active” treatments were subdivided into CBT, PE or other interventions. “Inactive” conditions were categorized as waitlist, TAU and attention-placebo conditions, those in which participants received no intervention during the trial period (Firth et al., 2017). No restrictions were placed on diagnosis or any other clinical or demographic characteristics of eligible samples, and participants were diverse PTSD victims including post-war PTSD, post-road accident PTSD, post-terrorist PTSD, etc. Only English-language articles were included. We selected studies for inclusion in a two-stage process. First, two independent reviewers (W.D. and D.H.) screened the titles and abstracts to identify eligible studies; this screening was followed by retrieval and assessment of the full texts of the relevant citations. Any disagreements were settled by discussion with a third reviewer (X.L.). This procedure is summarized in Fig. 1.

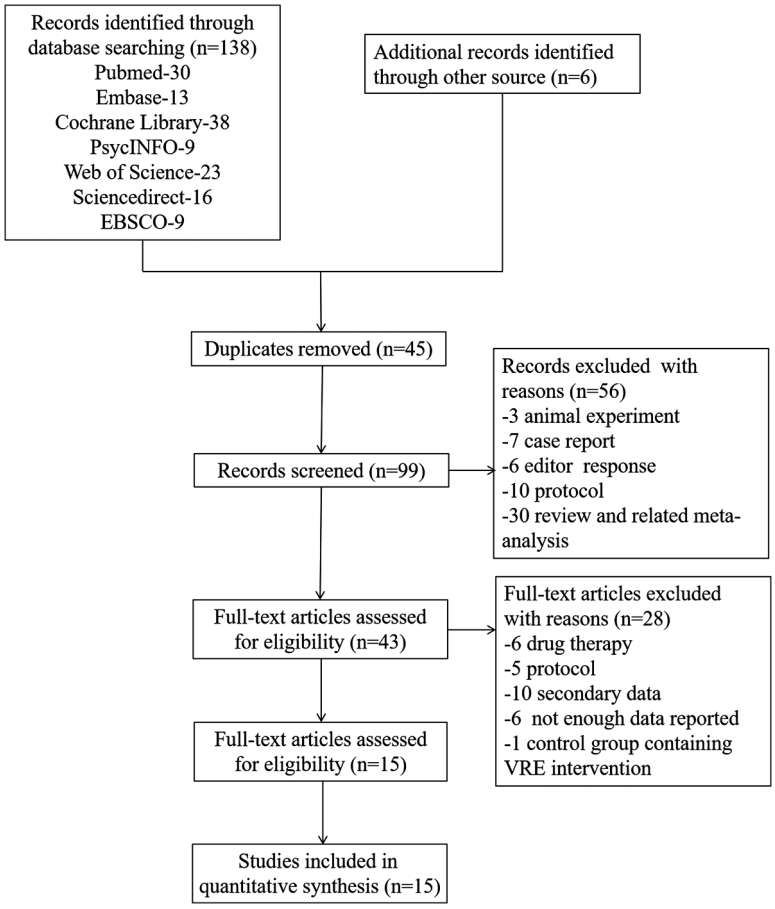


Fig. 1. PRISMA flow chart of study selection.

2.3. Quality assessment

We used the Cochrane risk of bias assessment tool (Higgins et al., 2011) to assess the methodological quality of RCTs, risk of bias in selection, performance, detection, attrition, and outcome reporting, ranking each area as high, low or unknown for risk of bias. Besides, we used the Newcastle-Ottawa Scale (Wells, 2000) to determine whether there was a risk for bias in the single-group trials studies related to selection and comparability of cohorts, and outcome. Two authors (W.D. and D.H.) evaluated the risk of bias for each domain independently. Studies were then further classified in an overall risk of bias category. A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

2.4. Data extraction

Data was extracted in duplicate (W.D. and D.H.) with standardized data extraction forms. We collected the following data: 1) characteristics of participants (sample size, mean age of participants and diagnostic information or relevant inclusion criteria); 2) intervention features (study length, trial quality, regularity of treatment, any additional intervention components, details of the control group); 3) effects on PTSD and depressive symptoms (changes in total PTSD and depressive symptoms scored of baseline, post-treatment and follow-up using any clinically validated rating scale). Study authors were contacted to clarify abstracted data and obtain patient-level data to ensure accuracy in the review. When the same trial was reported twice, we used the most recent study with the largest sample size for relevant outcomes. If a report did not provide enough data to calculate effect-sizes, we contacted its authors by e-mail to retrieve the data, and if the authors did not respond with sufficient outcome data or other missing characteristics after two contact-attempts, the studies were excluded. Disagreements between reviewers regarding data abstraction were resolved through discussion.

2.5. Statistical analysis

All analyses were conducted by Comprehensive Meta Analysis 2.0 (Pierce et al., 2008).

First, we conducted between-group analysis for RCTs, the total difference in changes in each PTSD symptoms outcome between VRET and control groups was pooled to compute the overall effect size using Hedges' g with 95% confidence intervals (CIs). Hedges' g is the index of effect adjusted for any pre-intervention differences between intervention and control groups, weighted by the inverse of its variance prior to any analysis and that provides a relatively unbiased standardized effect size estimate (Hedges and Olkin, 1985) based on small samples as compared to Cohen's d. Meanwhile, the heterogeneity test was conducted among the studies. $I^2 > 50\%$, $p \leq 0.05$, indicates a notable heterogeneity, and a random effect model was used. Otherwise, a fixed effect model was conducted. Furthermore, subgroup analysis of active and inactive groups was conducted.

Second, we explored the effect size of the depressive symptoms which were usually used as a secondary outcome measure for studying PTSD. Subgroup analysis of active and inactive groups was conducted as well.

Third, after between-group effect sizes of PTSD and depressive symptoms were computed, we used meta-regression to explore the dose–response relationship between the number of session and the

treatment effect.

Forth, we computed long-range effect size (change from post-treatment to 3-month follow-up; change from post-treatment to 6-month follow-up) for virtual reality-based conditions using Hedge's g. All effect sizes were calculated such that a positive value indicates a favorable outcome of VRET over the control (more symptom reduction). Less than 0.2 indicates a small effect, greater than 0.8 indicates a large effect, and an intermediate effect between 0.2 and 0.8, respectively (Hedges and Olkin, 1985).

Finally, rate meta-analysis was conducted for single-group trials. We defined "effective" as the decline in outcome measures compared to baseline, indicating a symptomatic relief or no longer meeting the PTSD diagnostic criteria. Then we directly calculated the ratio of the number of events to the total number of people as an effective rate.

2.6. Publication bias and additional analyses

The presence of publication bias was evaluated by drawing a funnel plot. And Egger's regression test was applied to adjust the aforementioned analyses. Additionally, we calculated the overall effect size of studies which had reported intent-to-treat or complete outcome data. Then we performed a subgroup analysis to find the source of heterogeneity. Additionally, for situations that the heterogeneity is too large, Duval and Tweedie's trim-and-fill analysis was conducted to re-calculate the pooled effect size after removing any studies which may introduce publication bias (i.e., small studies with large effect sizes from the positive side of the funnel plot) (Duval and Tweedie, 2000), and "fail-safe N" was used to account for the file draw problem (Orwin, 1983), estimating the number of negative results which would be required to invalidate the current meta-analysis.

3. Results

A preliminary search obtained 102 articles. Thirty-eight duplicate articles were removed. Six further articles were retrieved following an additional search. And then we read the title and abstract of the remaining 70 articles for preliminary screening. We excluded literatures with reasons including animal experiment, case report, editor response, protocol, review and related meta-analysis. Finally, full texts were retrieved for 42 papers, of which 18 met eligibility criteria, including 13 RCTs studies (n = 699) (Beidel et al., 2017; Botella et al., 2010; Difede et al., 2007, 2014; Gamito et al., 2010; McLay et al., 2010, 2017, 2011; Miyahira et al., 2012; Ready et al., 2010; Reger et al., 2016; Rothbaum et al., 2014; Roy et al., 2010) and 5 single-group trials studies (n = 60) (Beck et al., 2007; Ready et al., 2006; Rizzo et al., 2010; Wood et al., 2011; Zinzow et al., 2017). The literature screening process is shown in Fig. 1.

3.1. Characteristics of included studies

Full details of each study are displayed in Table 1. Outcome data were available from 18 studies including 13 RCTs with two or three arms and 5 single-group pre- and post-test trials with single arm. Three papers reported outcome data in a format not suited for meta-analysis, but the corresponding authors provided the raw data to enable inclusion (Gamito et al., 2010; Rothbaum et al., 2014; Roy et al., 2010). Mean sample ages ranged from 18 to 59 years (median 39 years). Patients in these studies were survivors of 9/11 WTC attacks (Difede et al., 2007), veterans and active duty military personnel with combat-related PTSD (Beidel et al., 2017; Difede et al., 2014; Gamito et al., 2010; McLay et al., 2010, 2017, 2011; Miyahira et al., 2012; Peskin et al., 2018a; Ready et al., 2010, 2006; Reger et al., 2016; Rizzo et al., 2010; Rothbaum et al., 2014; Roy et al., 2010; Wood et al., 2011), diverse trauma PTSD victims (Botella et al., 2010), MVA-related PTSD (motor vehicle accident) (Beck et al., 2007; Zinzow et al., 2017) that met Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revision (DSM–IV-TR) (APA, 2000) criteria for PTSD based on the Clinician-Administered PTSD Scale (Blake et al., 1995). Among them, there are two placebo-controlled studies on d-cycloserine augmentation of VRET for PTSD (Difede et al., 2014; Rothbaum et al., 2014), and one study compared Trauma Management Therapy (TMT; VRET plus a group treatment for anger, depression, and social isolation) vs. VRET plus a psychoeducation control condition (Beidel et al., 2017). VR exposure therapy lasted between 5 and 12 weeks. PTSD symptoms were measured as a primary outcome in all studies. Besides, depressive and anxiety symptoms were measured as secondary outcomes. The following tools were used: the Clinician Administered PTSD Scale (CAPS) (Blake et al., 1995), the PTSD Checklist (PCL) (Blanchard et al., 1996), the Beck Depression Inventory II (Beck et al., 1996).

3.2. Risk of bias assessment

Results from the Cochrane Risk of Bias assessments are displayed in Fig. 2. As stated in Fig. 2A, the frequent risk factor for bias was inadequate blinding of participants and personnel and allocation concealment, with only 5 of 13 studies using blind method for which the participants would not be aware of their treatment control status or of the hypothesized outcomes of the trial. Fig. 2B showed the risk of bias, mainly from the implementation of allocation concealment and lack of blinding. The five single-group trials had an average score of three stars for selection, one star for comparability, and three stars for ascertaining of the outcome and were regarded to have a low risk of bias.

3.3. Between-group effect size of VRET on PTSD symptoms

Fig. 3A displays the pooled effect size of VRET on posttraumatic symptoms change in comparison to control conditions. Meta-analysis revealed a moderate positive effect size of VRET for reducing posttraumatic symptoms compared to control groups (10 studies, n = 309, g = 0.327, 95% CI: 0.105–0.550, p < 0.01). There was moderate heterogeneity across the study data (p = 0.46 I^2 = 47.56%), so we chose a fix-effects model. The funnel plot is presented in Fig. 3B and Duval and Tweedie's trim-and-fill analysis identified no outlier studies. When only considering studies which used intention-to-treat analyses and/or reported complete outcome data, we found a similar effect of VRET on PTSD symptoms (8 studies, n = 215, g = 0.584, 95% CI: 0.318–0.850, p < 0.01).

3.4. Pre-planned subgroup analyses

In pre-planned subgroup analyses, we found that effect sizes were significantly greater when comparing VRET groups to inactive conditions than when using active control conditions (see Fig. 4 for the forest plot). When compared to inactive control conditions, VRET groups had a moderate positive effect on posttraumatic symptoms, and the pooled effect size across 5 VRET groups (n = 175) was g = 0.567 (95% CI: 0.270–0.863, p < 0.01).

However, when compared to active control conditions, there was no significant difference (6 studies, n = 239, g = 0.017, 95% CI: −0.412–0.445, p = 0.939). VRET groups and active control conditions had a comparable effect size on posttraumatic symptoms. Heterogeneity across the study data was not significant. It is worth mentioning that the between-subgroup effect size was significant (Q = 4.279, p = 0.039). We also applied another subgroup analyses to explore whether VRET was effective for different populations or not. The main population is war veterans with combat-related PTSD (9 studies, N = 348, g = −0.119, 95% CI: −0.350, 0.113 p > 0.05; Q = 12.95, I^2 = 38.244). There was no significant effect among different populations. See Table 2 for pre-planned subgroup effects of VRET on PTSD symptoms.

Table 1
Studies included in the Meta-analysis and their Characteristics intervention type, intervention length (sessions, duration, frequency), control group type.

Study	Sample type	Study design	N (each group)	Age (years,mean)	Design type	duration	control group type	Assess period	Outcome measure
Difede et al., 2007	Civilians and disaster workers directly exposed to the WTC attacks	RCT	10,8	40.92, 45.13	VRET	6–13 sessions	waitlist	Assessments occurred at pre-treatment, post-treatment, and at 6-month follow-up	CAPS BDI GSI
Gamito et al., 2010	Portuguese war veterans with war-related posttraumatic stress disorder	RCT	4,1,3	63.5	VRET	12 sessions	exposure in imagination (EI) waitlist	Assessed at pretreatment, he middle of treatment (5th session) and posttreatment	IES-R SCL-90R CAPS BDI
Botella et al., 2010	Diverse trauma PTSD victims	RCT	5,5	NA	CBT + VRET	9–12 sessions	CBT	Assessments occurred at pre-treatment and post-treatment	CAPS DTS PTCI
Ready et al., 2010	Vietnam veterans with war-related posttraumatic stress disorder (PTSD)	RCT	6,5	57,58	VRET	ten 90-minute individual psychotherapy sessions	PCT (present-centered therapy)	Assessments occurred at pre-treatment, post-treatment, and at 6-month follow-up	CAPS BDI
Roy et al., 2010	Military service members (SMs) who have been deployed to Iraq or Afghanistan	RCT	9,10	34	VRET	12 or more 90-min sessions over 6 weeks	PE	Assessments occurred at pre-treatment, post-treatment, and maintained at 3 months followup	CAPS CGI
McLay et al., 2010	Deployment-related PTSD in Camp FallujahIraq	Cohort	6,4	26.5, 24.5	VRET	Once or twice a week for 6 to 12 weeks	ET	Assessments occurred at pre-treatment, post-treatment	PCL-M BAI PHQ-9
McLay et al., 2011	Active Duty Service Members with Combat-Related Post-Traumatic Stress Disorder	RCT	10,10	28, 28.8	VR-GET	14 sessions	TAU (treatment as usual)	Assessments occurred at pre-treatment, post-treatment, and at 10–46 weeks to postassessment	CAPS
Miyahira et al., 2012	Active duty service members with PTSD symptoms	RCT	29,13	None	VRET	10 treatment sessions (2 once a week for 5 weeks	MA (minimal attention)	None	CAPS PDS BDI-II QOLI TRGI
Difede et al., 2014	People with chronic WTC-related PTSD	RCT	13,12	47.77, 43.75	VRET + D-cycloserine (100 mg)	12 sessions	placebo	Assessments occurred at pre-treatment, following sessions 3, 6, 10, post-treatment, and at 6 months.	CASP PCL BDI-II SCID-MDD STAXI-2
Rothbaum et al., 2014	Iraq and Afghanistan War Veterans with posttraumatic stress disorder (PTSD)	RCT	53,50,53	34.9, 36.2, 34.3	VRET + D-cycloserine (50 mg) /alprazolam (0.25 mg)	6 sessions	placebo	Assessments occurred at pre-treatment, post-treatment, and maintained at 3, 6, and 12 month follow-up	CAPS MINI PSS Cortisol and Startle assessments
Reger et al., 2016	Active duty soldiers with deployment-related posttraumatic stress disorder	RCT	54,54,54	29.52, 30.89, 30.39	VRET	10 sessions	PE waitlist	Assessments occurred at baseline, halfway through treatment, at posttreatment, and at 3- and 6-month follow-ups	CAPS PCL-C BDI-II BAI SSRPH IASMHS CSQ

(*continued on next page*)

Table 1 (*continued*)

Study	Sample type	Study design	N (each group)	Age (years,mean)	Design type	duration	control group type	Assess period	Outcome measure
Beidel et al., 2017	Iraq and Afghanistan veterans and active duty military personnel with combat-related PTSD	RCT	49,43	37.67, 33.26	Trauma Management Therapy (TMT; VRET plus a group treatment)	three times a week for 17 weeks	VRET plus a psychoeducation control condition	Assessments occurred at pre-, mid- and posttreatment, and at 3- and 6-month follow-up	CAPS PCL-M SCID I and II M-FAST CGI HAMD HAMA
McLay et al., 2017	Active duty military members with established diagnoses of PTSD related to service in Iraq or Afghanistan	RCT	43,38	33, 32	VRET	8 or 12 90-min sessions twice a week over 9 weeks	CET(control exposure therapy)	Assessed symptoms before treatment, one week after finishing treatment, and 3 months after completing treatment	CAPS
Ready et al., 2006	Vietnam veterans with posttraumatic stress disorder (PTSD)	Single-group trials	14	NA	VRET	two 90-minute individual therapy sessions per week	NONE	Assessments occurred at pre-treatment, post-treatment, and maintained at 3 and 6 month follow-up	CAPS IES BDI SUDS
Beck et al., 2007	Individuals with posttraumatic stress disorder symptoms after road accidents	Single-group trials	8	49.5	VRET	10-session treatment	NONE	Pretreatment assessment and a posttreatment assessment (1 month follow the last VRET session).	CAPS PSS-SR IES-R BDI-II BAI CSQ SSQ PQ SUDS
Rizzo et al., 2010	Active duty SMS redeployed from Iraq with posttraumatic stress disorder symptoms	Single-group trials	20	28	VRET	Twice a week, 90–120 min sessions over			
5 weeks	NONE	Assessments occurred at pre-treatment, post-treatment, and maintained at 3 month follow-up	PCL-M BAI PHQ-9						
Wood et al., 2011	Combat veterans with Post-Traumatic Stress Disorder	Single-group trials	12	36.3	VR-GET	10 sessions	NONE	Assessments occurred at pre-treatment, post-treatment	PCL-M BAI PHQ-9
Zinzow et al., 2017	Previously deployed service members who indicated moderate to high levels of driving anxiety, aggression or phobia	Single-group trials	6	38.7	VRET	Eight 90-minute sessions treatment	NONE	Assessments occurred at pre-treatment, post-treatment, and maintained at 1 monthfollow-up, and subsequent follow-up phone interview	PCL-5 SCID–Driving Phobia HDS ABPD DCQ

Abbreviations: BDI = Beck Depression Inventory, CAPS = Clinician-Administered Posttraumatic Stress Disorder Scale, GSI = Global Severity Inventory, PDS = PTSD Diagnostic Scale, BDI-II = Beck Depression Inventory II, QOLI = Quality of Life Inventory, TRGI = The Trauma Related Guilt Inventory, PCL-C = The PTSD Checklist, Civilian Version, BAI = The Beck Anxiety Inventory, SSRPH = Stigma Scale for Receiving Psychological Help, IASMHS = Inventory of Attitudes Toward Seeking Mental Health Services, CSQ = The Client Satisfaction Questionnaire, PCL-M = PTSD Checklist – Military Version, SCID I and II =Structured Clinical Interview for DSM-IV,M-FAST = Miller-Forensic Assessment of Symptoms Test, CGI = Clinical Global Impressions Scale, HAMD = Hamilton Rating Scale for Depression, HAMA = Hamilton Rating Scale for Anxiety, MINI = The Mini International Neuropsychiatric Interview, PSS = The PTSD Symptom Scale, SCID-MDD = SCID major depressive disorder, STAXI-2 = State-Trait Anger Expression Inventory-2, SSRPH = Stigma Scale for Receiving Psychological Help, IASMHS = Inventory of Attitudes Toward Seeking Mental Health Services, CSQ = The Client Satisfaction Questionnaire, CES = The Combat Exposure Scale, IES = The Impact of Event Scale, PGI = The patient rated version of the Clinical Global Impressions Scale, PSS-SR = Posttraumatic Stress Scale–Self Report, IES-R = The Impact of Event Scale–Revised, SSQ = The Simulator Sickness Questionnaire, PQ = The Presence Questionnaire, PHQ-9 = The Patient Health Questionnaire, DBS = The Driving Behavior Survey, HDS = The Hyperarousal in Driving Situations, ABPD = Anxiety-Based Performance Deficits, DCQ = Driving Cognitions Questionnaire (full scale), DTS = Davidson Trauma Scale, Posttraumatic Cognitions Inventory (PTCI).

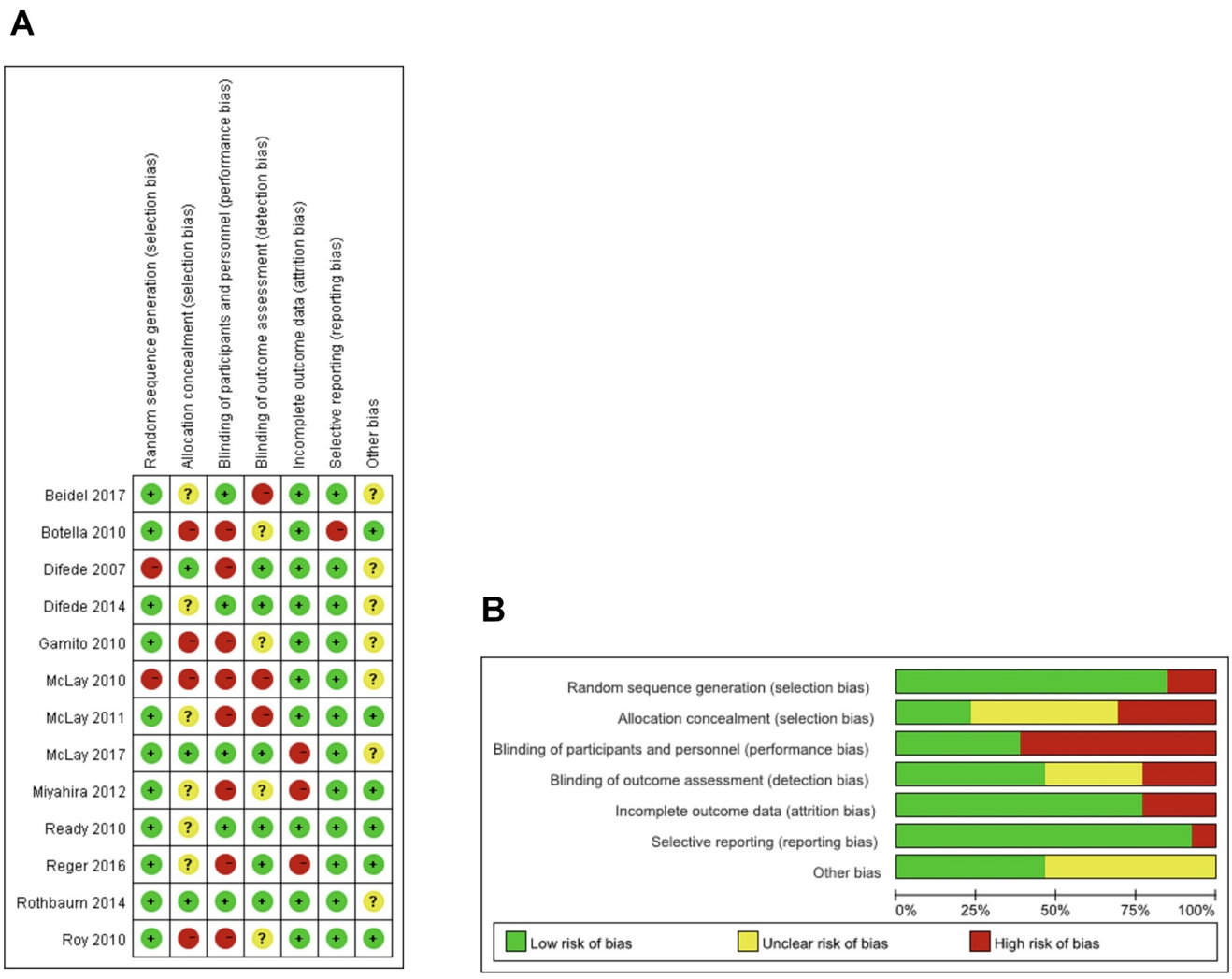


Fig. 2. Quality assessment of RCTs. (A) Risk of bias summary: review authors' judgments about each risk of bias item for each included study. (B) Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

3.5. Between-group effect size of VRET on depressive symptoms

We further compared the pooled effect size of VRET on depressive symptoms change to control conditions in a fix-effects model. Moderate pooled effect size was observed (7 studies, $n = 209$, $g = 0.373$, 95% CI: 0.110–0.637, $p < 0.01$) (see Fig. 5 for the forest plot). There was also a moderate heterogeneity across the study data ($p > 0.05$, $I^2 = 49.153$). It indicated that VRET significantly reduced participators' depressive symptoms compared to other interventions. Besides, subgroup analyses revealed that effect sizes were greater when comparing VRET to inactive conditions than when using active control conditions ($g_{active} = 0.124$, $p > 0.05$; $g_{inactive} = 0.548$, $p < 0.01$), but the between-subgroup effect size was not significant ($Q = 2.404$, $p = 0.121$).

3.6. Meta-regression analysis of VRET sessions

Meta-regression analysis showed a trend in the dose-response relationship as presented in Fig. 6 ($\beta = 0.133$, $p = 0.014$), which indicated more treatment sessions yielded larger effect sizes.

3.7. Long-range effect size of VRET on PTSD symptoms

The random effects model analysis showed that the pooled 3-month follow-up effect of the VRET groups was $g = 0.697$ (95% CI: 0.262–1.133, $p < 0.01$), compared with the post-treatment. The effect of the VRET group was maintained after 6-month and showed a sustained decrease on PTSD symptoms ($g = 0.848$, 95% CI: 0.324–1.372, $p < 0.01$). The forest plot is shown in Fig. 7.

3.8. Overall effects of single-group trials

In the five single-group trials of VR exposure treatment, 60 patients were involved in this assessment. With the pooled log(OR) values of 1.424 (95% CI: 0.779–2.069, $p < 0.001$) for overall analysis with insignificant heterogeneity, it was indicated that the VRET intervention had significant effect on PTSD (see forest plot in Fig. 8).

4. Discussion

As far as we know, this was the first meta-analysis to examine the efficacy of virtual reality exposure therapy (VRET) for PTSD. Eighteen studies met eligibility criteria, including 13 controlled studies ($n = 699$) and 5 uncontrolled studies ($n = 60$). Therefore, the literature base in this particular field has developed rapidly and the researches that we collected were comprehensive. Compared with the recent meta-analysis of VRET for anxiety, phobias or other interventions for PTSD (Gallegos et al., 2017; Kline et al., 2018; Opriş et al., 2012; Wolitzky-Taylor et al., 2008), more eligible interventions and participants in the current meta-analysis were identified. With the development of VR technology, more and more families or individuals have the

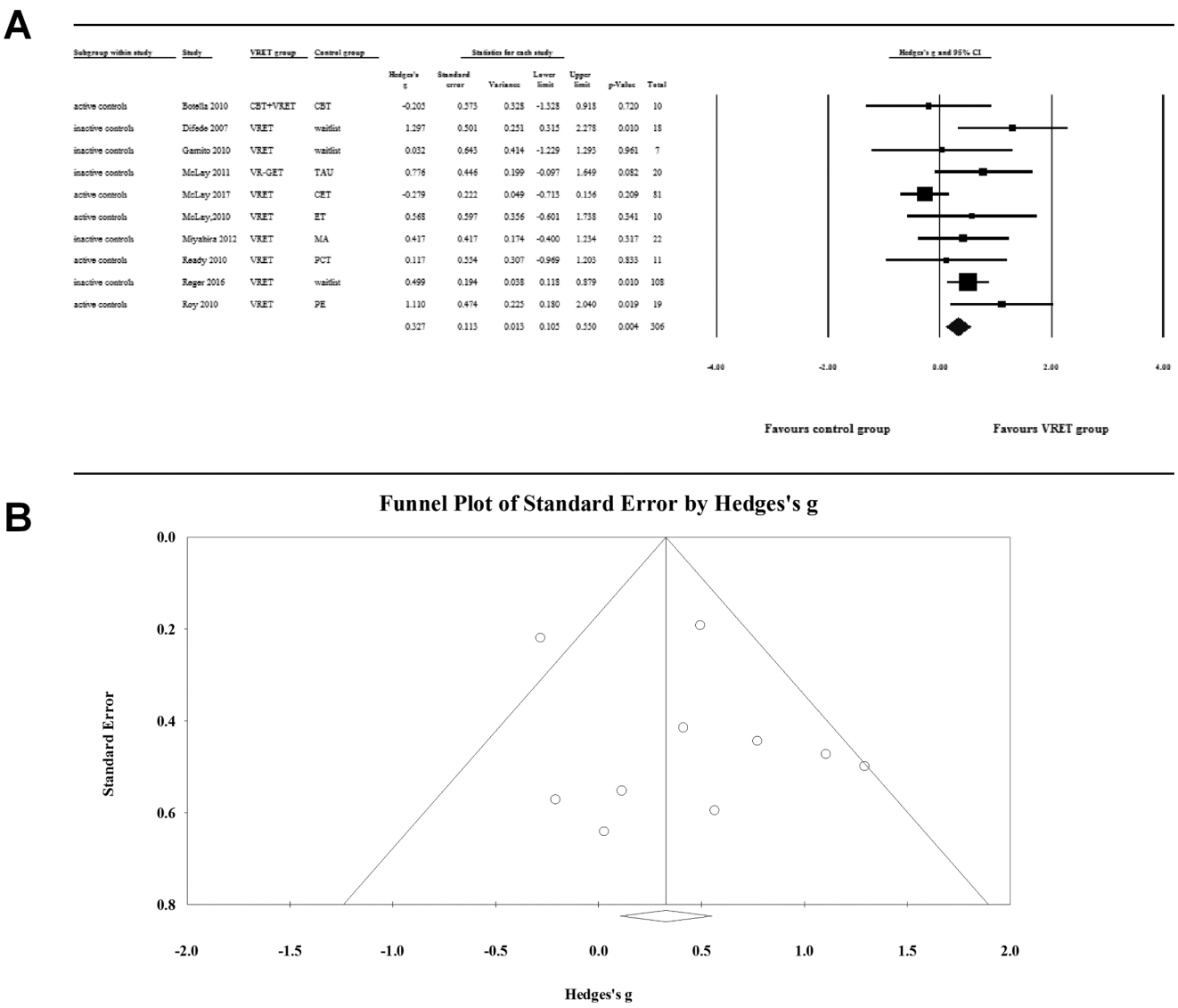


Fig. 3. Between-group effect size of VRET on PTSD symptoms. (A) Meta-analysis of the effects of VRET on PTSD symptoms. Box size represents study weighting. Diamond represents overall effect size and 95% CI. (B) Funnel plot of VRET vs. no VRET.

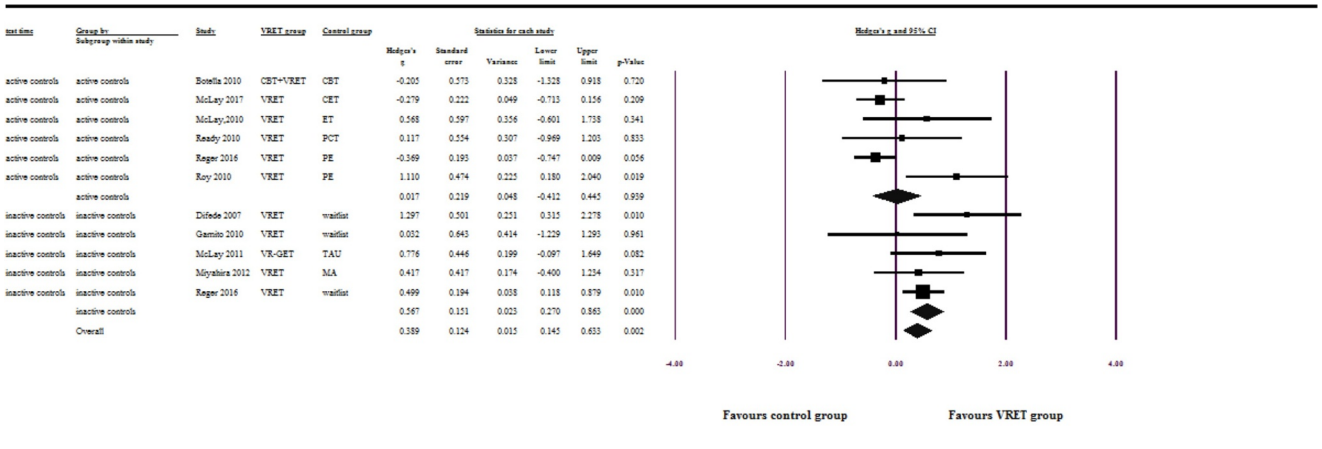


Fig. 4. Meta-analysis showing effects of VRET on PTSD symptom in comparison to active or inactive controls. Box size represents study weighting. Diamonds represent overall effect size and 95% CI.

Table 2
Effects of VRET on PTSD symptoms: pre-planned subgroup analyses.

Studies		Sample size (VRET/ control)	Meta- analysis Hedges' g	95% CI		p	Heterogeneity Q	p	I^2	Publication bias (Egger's regression) Intercept	p
Main analysis	10	159/147	0.327	0.105	0.550	0.004	17.162	0.046	47.560	0.874	0.425
Intent-to-treat or complete outcome data	8	111/104	0.584	0.318	0.850	0.000	5.243	0.630	0.000	0.279	0.734
VRET vs. active control	6	123/116	0.017	−0.412	0.445	0.939	10.369	0.065	51.781	2.100	0.104
VRET vs. inactive control	5	90/85	0.567	0.270	0.863	0.000	3.290	0.511	0.000	0.416	0.721
War veterans	9	172/176	−0.119	−0.350	0.113	0.057	12.95	0.113	38.244	1.473	0.305
Other population	2	15/13	0.737	−0.023	1.497	0.451	5.95	0.015	83.187	0.657	0.611

opportunity to experience or own this new technology, and its usage becomes more and more extensive. Furthermore, 15 of the 18 eligible studies were published within the last decade, which might reflect the VR technology development and the increased research interest in using VR technology to improve mental health (Lake, 2015).

The main analysis of 10 RCTs found that VRET had a moderate positive significant effect ($g = 0.327$) on PTSD symptoms, with relatively small heterogeneity and no indication of publication bias. Subgroup analysis revealed that the effects of VRET were substantially larger when compared to inactive ($g = 0.567$) groups than active ($g = 0.017$) control groups. However, there was an insignificant small effect size ($g = 0.017$) favoring VRET over in active conditions. It means VRET and traditional therapy had a comparable effect size on posttraumatic symptoms. Previous reviews of other technological interventions for mental health have reported similar findings (Kampmann et al., 2016; Opriş et al., 2012; Powers and Emmelkamp, 2008). For example, a meta-analysis of VR interventions for treating anxiety or social anxiety disorder found significant effects in comparison to inactive controls, but no difference from traditional psychological treatments (Opriş et al., 2012).

PTSD is often accompanied by depressive symptoms (Morina et al., 2013; Peskin et al., 2018b; Rytwinski et al., 2013). Thus we also evaluated the mitigating effect of VRET on depressive symptoms compared to other interventions. The result indicated a moderate pooled effect size ($g = 0.373$). Similar to the previous meta-analysis of mindfulness-based interventions for depressive disorder (Wang et al., 2018), subgroup analyses revealed larger effect when compared to inactive ($g = 0.548$) than active ($g = 0.124$) control conditions. We also explored population type factor which may influence the effects of VRET for posttraumatic symptoms. However, significant benefits of VRTE were not found for different population types. This may be due to the small sample sizes, as the majority of studies were conducted in combat-related PTSD populations, and other types of PTSD were rare. Anyway, this finding indicated that VRET may be applicable to a broad range of individuals.

The dose-response relationship was consistent with our prediction. The present study revealed that more sessions of VRET had a larger effect, that is to say, the number of sessions regulated the magnitude of the effect obtained from the VRET. Similar results were mentioned in previous meta-analysis studies using VRET to treat anxiety (Opriş et al., 2012; Powers and Emmelkamp, 2008). Therefore, it may be beneficial for more treatment sessions of VRET to be utilized.

The long-range effect size of VRET on PTSD symptoms showed a sustained decrease at 3-month follow-up ($g = 0.697$) and at 6-month follow-up ($g = 0.848$), which findings indicated that VRET could produce significant and long-term PTSD symptom change in real-life situations and supported its application in treating PTSD. There were two placebo-controlled studies on D-cycloserine (DCS) augmentation of VRET for PTSD (Difede et al., 2014; Rothbaum et al., 2014), and the DCS showed a tendency of enhancing exposure effect at the end of treatment ($g = 0.272$, $p = 0.118$), though the corresponding p-value is non-significant. Nevertheless, the treatment effect of DCS subsided at 6-months follow-up ($g = -0.635$). Similar finding was reported in a meta-analysis about DCS augmentation of exposure-based cognitive behavior therapy for anxiety (Mataix-Cols et al., 2017). It is necessary to identify the potential moderating variables associated with DCS response in further research.

Furthermore, overall effects of single-group trials also revealed that VRET had a significantly positive effect on PTSD with the pooled log (OR) values of 1.424 ($p < 0.001$). Therefore, the meta-analysis of random and single-group trials collectively suggested that VRET was effective in treating PTSD. Although there was a significant difference in the overall effect sizes when comparing RCTs to single-group trials, we have to say, single-group trials design seems to make the dropout rate decreased, albeit modest. More importantly, the meta-analysis that included both RCTs and single-group trials could broaden the results and increase the applicability of our findings. There is evidence that the estimates from the superior quality single-group trials may be similar to the RCTs (Faber et al., 2016). We have conducted some fundamental methodological components of the systematic review process

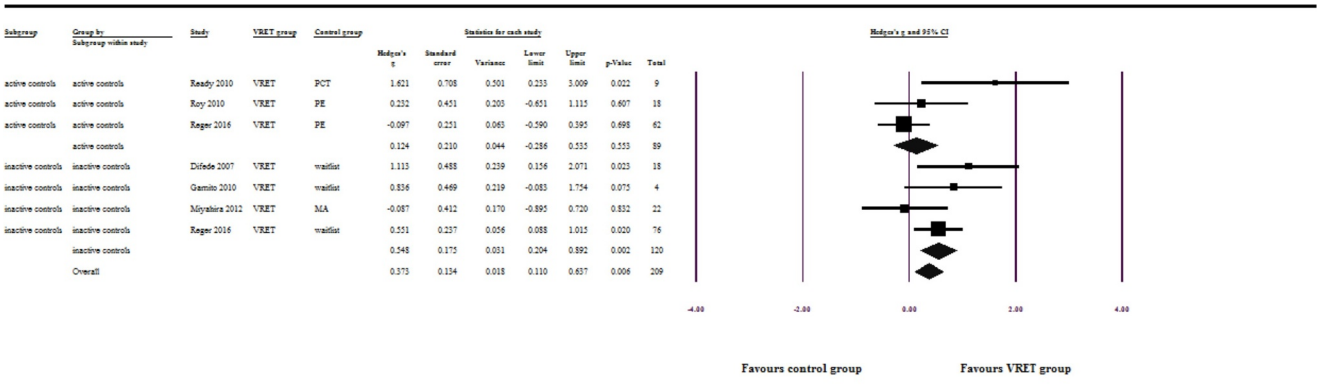


Fig. 5. Meta-analysis showing effects of VRET on depressive symptom in comparison of active and inactive controls. Box size represents study weighting. Diamond represents overall effect size and 95% CI.

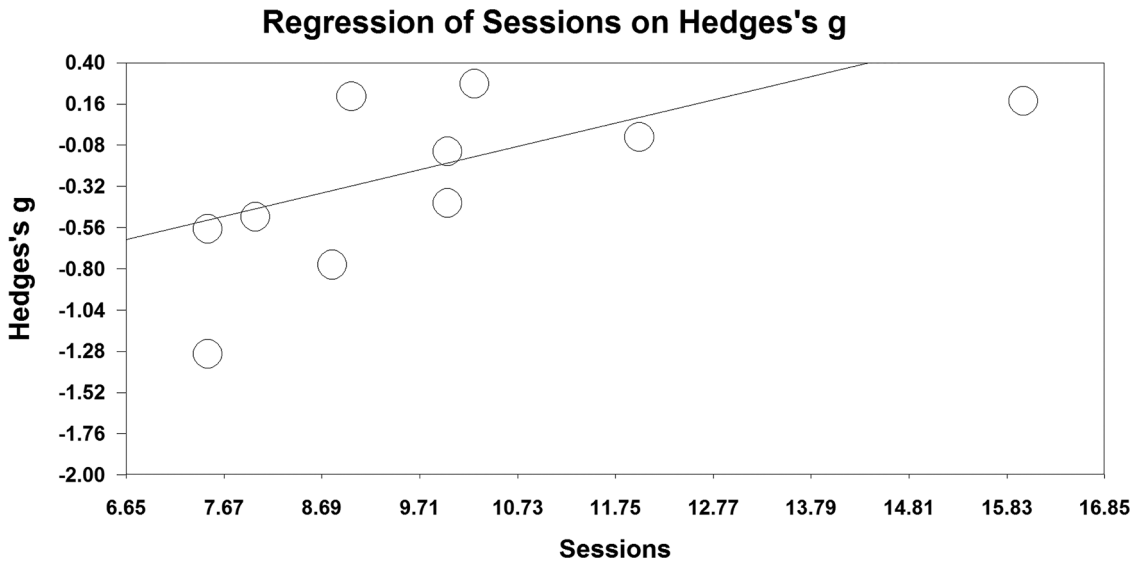


Fig. 6. Dose–response regression.

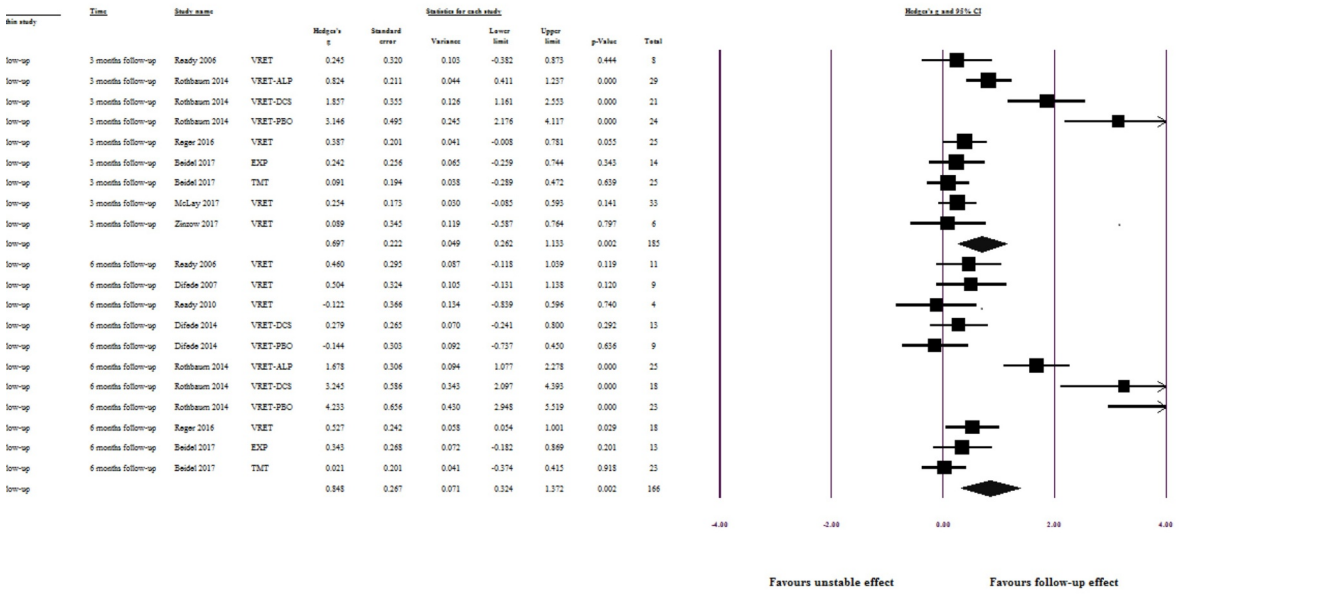
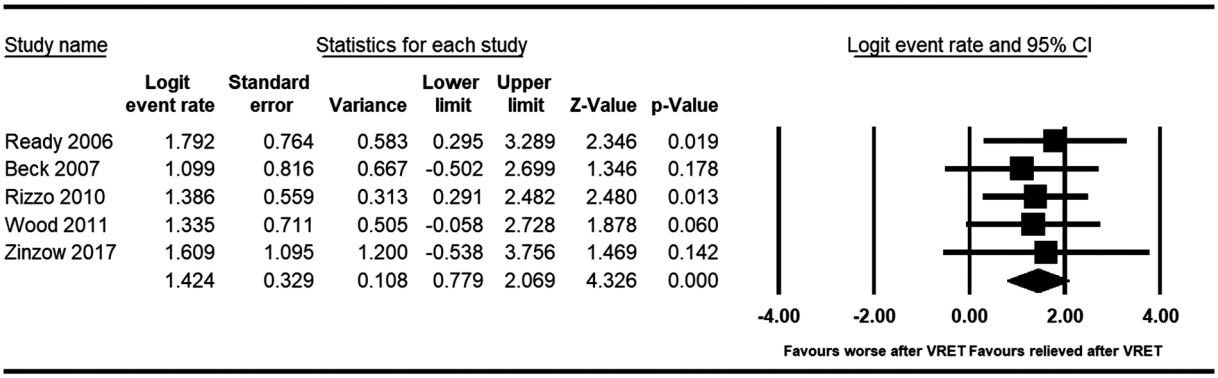


Fig. 7. Long-range effect size (change from post-treatment to 3 month follow-up; change from post-treatment to 6 month follow-up). Box size represents study weighting. Diamond represents overall effect size and 95% CI.



Study name	Logit event rate	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Ready 2006	1.792	0.764	0.583	0.295	3.289	2.346	0.019
Beck 2007	1.099	0.816	0.667	-0.502	2.699	1.346	0.178
Rizzo 2010	1.386	0.559	0.313	0.291	2.482	2.480	0.013
Wood 2011	1.335	0.711	0.505	-0.058	2.728	1.878	0.060
Zinzow 2017	1.609	1.095	1.200	-0.538	3.756	1.469	0.142
	1.424	0.329	0.108	0.779	2.069	4.326	0.000

Fig. 8. Rate meta-analysis of five single-group trials. Meta-analysis of the effects of VRET on PTSD symptoms. Box size represents study weighting. Diamond represents overall effect size and 95% CI.

description of the type of single-group trials included and assessment of risk of confounding bias in meta-analyses to make our results comprehensive and objective.

In general, VRET, technology-assisted interventions, based on CBT and exposure therapy significantly reduced posttraumatic and depressive symptoms. As a typically prevalent chronic disorder, PTSD was always associated with significant personal distress and functional impairment in lots of domains (Goncalves et al., 2012). Though there are many ways to treat PTSD, treatments that can effectively reduce the impact of the disease were limited. Nowadays, with the development of technology, the cost of using VR technology is getting lower and lower, and it is becoming more and more popular in therapy (Reger et al., 2018). Its trauma-related, multi-sensory stimulation ability is beneficial to increase the emotional engagement and real time presentation of multiple sensory stimulation can augment a patient's imaginative exposure (Bloch et al., 2013). To sum up, this novel treatment is effective, there is room for improvement, utilization of VRET for the situation that clinicians' experience is low, and patients' attrition rates are high. In future studies, the impact of the use of VR devices alone rather than other psychotherapeutic approaches to mental health should be examined and quantified to further explore the treatment efficacy of VRET.

5. Limitations

There are a few limitations in the current study. Firstly, most of the subjects in these studies were veterans whose PTSD caused by combat problems while PTSD patients may be diverse. Despite the fact that the problems are not the sources of heterogeneous, the differences among these PTSD may suggest that our conclusions should be interpreted with caution. Secondly, some studies in this meta-analysis are considered high-risk of bias (Botella et al., 2010; McLay et al., 2010), as they did not do adequate allocation concealment and blinding which suggests caution in interpreting these findings. Thirdly, to identify the potential moderating variables associated with interventions, something more detail about the experimental design, demographics, the number of intervention sessions, or the severity of PTSD needed to be collected. However, due to the limited data that could be collected, we were unable to perform subgroup analysis on these factors one by one. It might have a certain impact on the statistical results. In the future, it will be necessary to implement a more standard data reporting format to facilitate the full use of research data, thereby enhancing the reliability and validity of meta-analysis.

6. Conclusion

In conclusion, VRET is effective in treating PTSD. Though it is not absolutely better than traditional therapies, it also reduces PTSD and depression symptoms. Moreover, a dose–response relationship existed with more VRET sessions showing larger effects. In addition, VRET has a sustainable therapeutic effect and does not have a so-called dependence or withdrawal response similar to some drugs. These meta-analytic results contribute to the literature on VRET for PTSD symptoms, though there are numerous aspects of VRET worth exploring.

Contributors

Wenrui Deng : data processing and writing a paper;

Die Hu, Sheng Xu and Xiaoyu Liu: assessment of the full texts of the relevant citations;

Jingwen Zhao, Qian Chen, Bin Zhang and Zheng Zhang: retrieval and assessment of the title and abstract of the relevant citations;

Jiayuan Liu, Lijun Ma, Xinyi Hong and Wenxiu Jiang: search literature;

Shengrong Cheng and Boya Liu: quality assessment of each study;

Xiaoming Li: guide the study and modify this paper.

Declaration of Competing Interest

The authors state that there are no any conflict interests in the current literature.

Funding sources

This work was supported by the Anhui Natural Science Foundation (1808085MH291), and the project of Human Social Science of Anhuiprovince (SK2016A047), and Grants for Scientific Research of BSKY (XJ201826) from Anhui Medical University.

Acknowledgements

We thank Barbara OlasovRothbaum, Matthew price, Michael J. Roy and Pedro Gamito for providing the raw data of their research and giving us helpful feedback.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2019.07.086.

References

APA, 2013. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). American Psychiatric Pub.

APA, 2000. Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text rev. Author, Washington, DC.

Beck, A.T., Steer, R.A., Brown, G.K., 1996. Manual for the Beck Depression Inventory II. Psychological Corporation, San Antonio.

Beck, J.G., Palyo, S.A., Winer, E.H., Schwagler, B.E., Ang, E.J., 2007. Virtual reality exposure therapy for PTSD symptoms after a road accident: an uncontrolled case series. Behav. Ther. 38, 39–48.

Beidel, D.C., Frueh, B.C., Neer, S.M., Bowers, C.A., Trachik, B., Uhde, T.W., Grubaugh, A., 2017. Trauma management therapy with virtual-reality augmented exposure therapy for combat-related PTSD: a randomized controlled trial. J. Anxiety Disord.

Benbow, A.A., Anderson, P.L., 2019. A meta-analytic examination of attrition in virtual reality exposure therapy for anxiety disorders. J. Anxiety Disord. 61, 18–26.

Bisson, J.I., Ehlers, A., Matthews, R., Pilling, S., Richards, D., Turner, S., 2007. See comment. Br. J. Psychiatry 190, 97–104.

Blake, D., Weathers, F., Nagy, L., Kaloupek, D., Gusman, F., Charney, D., Keane, T., 1995. The development of a clinician-administered PTSD scale. J. Trauma Stress 8, 75–90.

Blanchard, E., Jones-Alexander, J., Buckley, T., Forneris, C., 1996. Psychometric properties of the PTSD checklist (PCL). Behav. Res. Ther. 34, 669–673.

Bloch, F., Rigaud, A.S., Kemoun, G., 2013. Virtual reality exposure therapy in posttraumatic stress disorder: a brief review to open new opportunities for post-fall syndrome in elderly subjects. Eur. Geriatr. Med. 4, 427–430.

Botella, C., Baños, R., Perpiñá, C., Villa, H., Alcañiz, M., Rey, A., 1998. Virtual reality treatment of claustrophobia: a case report. Behav. Res. Ther. 36, 239–246.

Botella, C., García-Palacios, A., Guillen, V., Baños, R.M., Quero, S., Alcaniz, M., 2010. An adaptive display for the treatment of diverse trauma PTSD victims. CyberPsychol. Behav 091220090754060.

Cadth, 2014. Virtual reality exposure therapy for adults with post-traumatic stress disorder: a review of the clinical effectiveness (Structured abstract), health technology assessment database. Can. Agen. Drug Tech. Health (CADTH).

Carlin, A., Hoffman, H., Weghorst, S., 1997. Virtual reality and tactile augmentation in the treatment of spider phobia: a case report. Behav. Res. Ther. 35, 153–158.

Cottraux, J., Note, I., Yao, S.N., de Mey-Guillard, C., Bonasse, F., Djamoussian, D., Mollard, E., Note, B., Chen, Y., 2008. Randomized controlled comparison of cognitive behavior therapy with rogerian supportive therapy in chronic post-traumatic stress disorder: a 2-year follow-up. Psychother. Psychosom. 77, 101–110.

Cukor, J., Spitalnick, J., Difede, J., Rizzo, A., Rothbaum, B.O., 2009. Emerging treatments for PTSD. Clin. Psychol. Rev. 29, 715–726.

Difede, J., Cukor, J., Jayasinghe, N., Patt, I., Jedel, S., Spielman, L., Giosan, C., Hoffman, H.G., 2007. Virtual reality exposure therapy for the treatment of posttraumatic stress disorder following September 11, 2001. J. Clinic. Psychiat. 1639–1647.

Difede, J., Cukor, J., Wyka, K., Olden, M., Hoffman, H., Lee, F.S., Altemus, M., 2014. D-cycloserine augmentation of exposure therapy for post-traumatic stress disorder: a pilot randomized clinical trial. Neuropsychopharmacology 1052–1058.

Duval, S., Tweedie, R., 2000. Trim and fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. Biometrics 56, 455–463.

Faber, T., Ravaud, P., Riveros, C., Perrodeau, E., Dechartres, A., 2016. Meta-analyses including non-randomized studies of therapeutic interventions: a methodological review. BMC Med. Res. Methodol. 16, 35.

Firth, J., Torous, J., Nicholas, J., Carney, R., Pratap, A., Rosenbaum, S., Sarris, J., 2017. The efficacy of smartphone-based mental health interventions for depressive symptoms: a meta-analysis of randomized controlled trials. World Psychiatry 16, 287–298.

Foa, E., McLean, C., Zang, Y., Rosenfield, D., Yadin, E., Yarvis, J., Mintz, J., Young-McCaughan, S., Borah, E., Dondanville, K., Fina, B., Hall-Clark, B., Lichner, T., Litz, B., Roache, J., Wright, E., Peterson, A., 2018. Effect of prolonged exposure therapy delivered over 2 weeks vs 8 weeks vs present-centered therapy on PTSD symptom severity in military personnel: a randomized clinical trial. JAMA 319, 354–364.

Foa, E.B., Davidson, R.T., Frances, A., 1999. The expert consensus guideline series. Treatment of posttraumatic stress disorder. The expert consensus panels for PTSD. J. Clin. Psychiatry 60 (Suppl 16), 3–76.

Foa, E.B., Rothbaum, B.O., Furr, J.M., 2003. Augmenting exposure therapy with other CBT procedures. Psychiatr. Ann. 33, 47–53.

Gallegos, A., Crean, H., Pigeon, W., Heffner, K., 2017. Meditation and yoga for post-traumatic stress disorder: a meta-analytic review of randomized controlled trials. Clin. Psychol. Rev. 58, 115–124.

Gamito, P., Oliveira, J., Rosa, P., Morais, D., Duarte, N., Oliveira, S., Saraiva, T., 2010. PTSD elderly war veterans: a clinical controlled pilot study. CyberPsychol. Behav 091220084725062.

Gerardi, M., Cukor, J., Difede, J., Rizzo, A., Rothbaum, B., 2010. Virtual reality exposure therapy for post-traumatic stress disorder and other anxiety disorders. Curr. Psychiatry Rep. 12, 298–305.

Gerardi, M., Rothbaum, B., Ressler, K., Heekin, M., Rizzo, A., 2008. Virtual reality exposure therapy using a virtual Iraq: case report. J. Trauma Stress 21, 209–213.

Goncalves, R., Pedrozo, A.L., Coutinho, E.S., Figueira, I., Ventura, P., 2012. Efficacy of virtual reality exposure therapy in the treatment of PTSD: a systematic review. PLoS ONE 7, e48469.

Hedges, L.V., Olkin, I., 1985. Statistical Methods for Meta-Analysis. Academic Press, Orlando.

Higgins, J.P.T., Green, S., 2011. Cochrane handbook for systematic reviews of interventions version 5.1.0. The Cochrane Collaboration [updated March 2011] 2011. Available from. www.cochrane-handbook.org.

Hosono, S., Arimoto, Y., Ohtani, H., 2006. Meta-analysis of short-term out- comes after laparoscopy-assisted distal gastrectomy. World J. Gastroenterol. WJG 12, 7676–7683.

Jorge, R.E., 2015. Posttraumatic stress disorder. CONTINUUM Lifelong Learn. Neurol. 21, 789–805.

Kampmann, I., Emmelkamp, P., Morina, N., 2016. Meta-analysis of technology-assisted interventions for social anxiety disorder. J. Anxiety Disord. 42, 71–84.

Kessler, R., Avenevoli, S., Costello, J., Green, J., Gruber, M., McLaughlin, K., Petukhova, M., Sampson, N., Zaslavsky, A., Merikangas, K., 2012. Severity of 12-month DSM-IV disorders in the national comorbidity survey replication adolescent supplement. Arch. Gen. Psychiatry 69, 381–389.

Kline, A., Cooper, A., Rytwinksi, N., Feeny, N., 2018. Long-term efficacy of psychotherapy for posttraumatic stress disorder: a meta-analysis of randomized controlled trials. Clin. Psychol. Rev. 59, 30–40.

Koenen, K.C., Ratanatharathorn, A., Ng, L., McLaughlin, K.A., Bromet, E.J., Stein, D.J., Karam, E.G., Ruscio, A.M., Benjet, C., Scott, K., 2017. Posttraumatic stress disorder in the world mental health surveys. Psychol. Med. 47, 2260–2274.

Lake, J., 2015. The integrative management of PTSD: a review of conventional and CAM approaches used to prevent and treat PTSD with emphasis on military personnel. Adv. Integrat. Med. 2, 13–23.

Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gotzsche, P.C., Ioannidis, J.P., Clarke, M., Devereaux, P.J., Kleijnen, J., Moher, D., 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J. Clin. Epidemiol. 62, e1–34.

Mataix-Cols, D., Fernández de la Cruz, L., Monzani, B., Rosenfield, D., Andersson, E., Pérez-Vigil, A., Frumento, P., de Kleine, R., Difede, J., Dunlop, B., Farrell, L., Geller, D., Gerardi, M., Guastella, A., Hofmann, S., Hendriks, G., Kushner, M., Lee, F., Lenze, E., Levinson, C., McConnell, H., Otto, M., Plag, J., Pollack, M., Ressler, K., Rodebaugh, T., Rothbaum, B., Scheeringa, M., Siewert-Siegmund, A., Smits, J., Storch, E., Ströhle, A., Tart, C., Tolin, D., van Minnen, A., Waters, A., Weems, C., Wilhelm, S., Wyka, K., Davis, M., Rück, C., Altemus, M., Anderson, P., Cukor, J., Finck, C., Geffken, G., Golfels, F., Goodman, W., Gutner, C., Heyman, I., Jovanovic, T., Lewin, A., McNamara, J., Murphy, T., Norrholm, S., Thuras, P., 2017. D-cycloserine augmentation of exposure-based cognitive behavior therapy for anxiety, obsessive-compulsive, and posttraumatic stress disorders: a systematic review and meta-analysis of individual participant data. JAMA Psychiatry 74, 501–510.

MacLehose, R.R., Reeves, B.C., Harvey, I.M., 2000. A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies. Health Technol. Assess. (Rockv) 4, 1–154.

McDonagh, A., Friedman, M., McHugo, G., Ford, J., Sengupta, A., Mueser, K., Demment, C.C., Fournier, D., Schnurr, P.P., Descamps, M., 2005. Randomized trial of cognitive-behavioral therapy for chronic posttraumatic stress disorder in adult female survivors of childhood sexual abuse. J. Consult. Clin. Psychol. 73, 515–524.

McLay, R., McBrien, C., Wiederhold, B., Wiederhold, B., 2010. Exposure therapy with and without virtual reality to treat PTSD while in the combat theater: a parallel case series. Cyberpsychol. Behav. Soc. Network.

McLay, R.N., Baird, A., Webb-Murphy, J., Deal, W., Tran, L., Anson, H., Klam, W., Johnston, S., 2017. A randomized, head-to-head study of virtual reality exposure therapy for posttraumatic stress disorder. Cyberpsychol. Behav. Soc. Netw. 218–224.

McLay, R.N., Wood, D.P., Webb-Murphy, J.A., Spira, J.L., Wiederhold, M.D., Pyne, J.M., Wiederhold, B.K., 2011. A randomized, controlled trial of virtual reality-graded exposure therapy for post-traumatic stress disorder in active duty service members with combat-related post-traumatic stress disorder. Cyberpsychol. Behav. Soc. Netw. 223–229.

Miyahira, S.D., Folen, R.A., Hoffman, H.G., Garcia-Palacios, A., Spira, J.L., Kawasaki, M., 2012. The effectiveness of VR exposure therapy for PTSD in returning warfighters. Stud. Health Technol. Inform. 128–132.

Monson, C., Schnurr, P., Resick, P., Friedman, M., Young-Xu, Y., Stevens, S., 2006. Cognitive processing therapy for veterans with military-related posttraumatic stress disorder. J. Consult. Clin. Psychol. 74, 898–907.

Morina, N., Ajdukovic, D., Bogic, M., Franciskovic, T., Kucukalic, A., Lecic-Tosevski, D., Morina, L., Popovski, M., Priebe, S., 2013. Co-occurrence of major depressive episode and posttraumatic stress disorder among survivors of war: how is it different from either condition alone? J. Clin. Psychiatry 74, e212–e218.

Opriş, D., Pintea, S., García-Palacios, A., Botella, C., Szamosközi, Ş., David, D., 2012. Virtual reality exposure therapy in anxiety disorders: a quantitative meta-analysis. Depress. Anxiety 29, 85–93.

Orwin, R.G., 1983. A fail-safe N for effect size in meta-analysis. J. Edu. Stat. 8, 157–159.

Peskin, M., Wyka, K., Cukor, J., Olden, M., Altemus, M., Lee, F., Difede, J., 2018a. The relationship between posttraumatic and depressive symptoms during virtual reality exposure therapy with a cognitive enhancer. J. Anxiety Disord.

Peskin, M., Wyka, K., Cukor, J., Olden, M., Altemus, M., Lee, F.S., Difede, J., 2018b. The relationship between posttraumatic and depressive symptoms during virtual reality exposure therapy with a cognitive enhancer. J. Anxiety Disord.

Pierce, C.A., Borenstein, M., Hedges, L.V., Higgins, J.P.T., Rothstein, H.R., 2008. (2005). Comprehensive Meta-Analysis (Version 2.0) [Computer Software] 11. Biostat. Organizational Research Methods, Englewood, NJ, pp. 188–191.

Powers, M., Emmelkamp, P., 2008. Virtual reality exposure therapy for anxiety disorders: a meta-analysis. J. Anxiety Disord. 22, 561–569.

Powers, M., Halpern, J., Ferenschak, M., Gillihan, S., Foa, E., 2010. A meta-analytic review of prolonged exposure for posttraumatic stress disorder. Clin. Psychol. Rev. 30, 635–641.

Ready, D.J., Gerardi, R.J., Backscheider, A.G., Mascaro, N., Rothbaum, B.O., 2010. Comparing virtual reality exposure therapy to present-centered therapy with 11 U.S. Vietnam veterans with PTSD. Cyberpsychol. Behav. Soc. Network. 49–54.

Ready, D.J., Pollack, S., Rothbaum, B.O., Alarcon, R.D., 2006. Virtual reality exposure for veterans with posttraumatic stress disorder. J. Aggress. Maltreat. Trauma 12, 199–220.

Reger, G.M., Koenen-Woods, P., Zetocha, K., Smolenski, D.J., Holloway, K.M., Rothbaum, B.O., Difede, J.A., Rizzo, A.A., Edwards-Stewart, A., Skopp, N.A., Mishkind, M., Reger, M.A., Gahm, G.A., 2016. Randomized controlled trial of prolonged exposure using imaginal exposure vs virtual reality exposure in active duty soldiers with deployment-related posttraumatic stress disorder (PTSD). J. Consult. Clin. Psychol no pagination2016.

Reger, G.M., Smolenski, D., Norr, A., Katz, A., Buck, B., Rothbaum, B.O., 2018. Does virtual reality increase emotional engagement during exposure for PTSD? Subjective distress during prolonged and virtual reality exposure therapy. J. Anxiety Disord.

Rizzo, A.S., Difede, J., Rothbaum, B.O., Reger, G., Spitalnick, J., Cukor, J., McLay, R., 2010. Development and early evaluation of the virtual Iraq/Afghanistan exposure therapy system for combat-related PTSD. Ann. N. Y. Acad. Sci. 1208, 114–125.

Rothbaum, B., 2009. Using virtual reality to help our patients in the real world. Depress. Anxiety 26, 209–211.

Rothbaum, B., Rizzo, A., Difede, J., 2010. Virtual reality exposure therapy for combat-related posttraumatic stress disorder. Ann. N. Y. Acad. Sci. 1208, 126–132.

Rothbaum, B.O., Hodges, L.F., 1999. The use of virtual reality exposure in the treatment of anxiety disorders. Behav. Modif. 23, 507.

Rothbaum, B.O., Price, M., Jovanovic, T., Norrholm, S.D., Gerardi, M., Dunlop, B., Davis, M., Bradley, B., Duncan, E.J., Rizzo, A., Ressler, K.J., 2014. A randomized, double-blind evaluation of D-cycloserine or alprazolam combined with virtual reality exposure therapy for posttraumatic stress disorder in Iraq and Afghanistan war veterans. Am. J. Psychiatry 640–648.

Roy, M.J., Francis, J., Friedlander, J., Banks-Williams, L., Lande, R.G., Taylor, P., Blair, J., McLellan, J., Law, W., Tarpley, V., Patt, I., Yu, H., Mallinger, A., Difede, J., Rizzo, A., Rothbaum, B., 2010. Improvement in cerebral function with treatment of posttraumatic stress disorder. Ann. N. Y. Acad. Sci. 142–149.

Rytwinski, N.K., Scur, M.D., Feeny, N.C., Youngstrom, E.A., 2013. The co-occurrence of major depressive disorder among individuals with posttraumatic stress disorder: a meta-analysis. J. Trauma. Stress 26, 299–309.

Wang, Y., Li, X., Zheng, W., Xu, Z., Ng, C., Ungvari, G., Yuan, Z., Xiang, Y., 2018. Mindfulness-based interventions for major depressive disorder: a comprehensive meta-analysis of randomized controlled trials. J. Affect. Disord. 229, 429–436.

Wells, G., 2000. Proceedings or the third symposium on systematic reviews beyond the basics. SBOD. Improving quality and impact, the Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analysis. Oxford.

Wolitzky-Taylor, K., Horowitz, J., Powers, M., Telch, M., 2008. Psychological approaches in the treatment of specific phobias: a meta-analysis. Clin. Psychol. Rev. 28, 1021–1037.

Wood, D.P., Webb-Murphy, J., McLay, R.N., Wiederhold, B.K., Spira, J.L., Johnston, S., Koffman, R.L., Wiederhold, M.D., Pyne, J., 2011. Reality graded exposure therapy with physiological monitoring for the treatment of combat related post traumatic stress disorder: a pilot study. Stud. Health Technol. Inform. 163, 696–702.

Yakoub, D., Athanasiou, T., Tekkis, P., 2009. Laparoscopic assisted distal gas- trectomy for early gastric cancer: is it an alternative to the open approach? Ann. Surg. Oncol. 18, 322–333.

Zinzow, H.M., Brooks, J.O., Rosopa, P.J., Jeffirs, S., Jenkins, C., Seeanner, J., McKeeman, A., Hodges, L.F., 2017. Virtual reality and cognitive-behavioral therapy for driving anxiety and aggression in veterans: a pilot study. Cogn. Behav. Pract.