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Review article

Efficacy of immersive PTSD treatments: A systematic review of virtual and augmented reality exposure therapy and a meta-analysis of virtual reality exposure therapy

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ABSTRACT

Background: Virtual reality exposure therapy (VRET) and augmented reality exposure therapy (ARET) are digitally assisted psychotherapies that potentially enhance posttraumatic stress disorder (PTSD) treatment by increasing a patient's sense of presence during exposure therapy. This study aimed to systematically review current evidence regarding the efficacy of VRET and ARET as PTSD treatment.

Methods: A systematic electronic database search, a systematic quality assessment and two meta-analyses were conducted in accordance with PRISMA guidelines.

Results: Eleven studies on the efficacy of VRET for PTSD ($n = 438$) were found, but no studies on the efficacy of ARET. The majority of VRET studies were of a low quality and had heterogeneous results. Meta-analyses showed VRET outperformed waitlist control (standardized mean difference −0.64 (95% CI -1.05 to −0.22)) while no significant difference was found between VRET and active treatment conditions (standardized mean difference −0.25 (95% CI −0.77 to 0.27)).

Conclusion: VRET was superior to waitlist control groups and as effective as other psychotherapies. However, the results showed considerable heterogeneity due to the low number of studies and variety of VRET methods. VRET may be an effective alternative to current treatments and shows promise for the treatment of PTSD patients that have not responded to previous treatment. Future research should focus on high quality RCTs, including information on side effects and adverse events, with sufficient numbers of participants. This study recognizes a research gap regarding the efficacy of ARET, while it may have potential for PTSD treatment.

1. Introduction

Posttraumatic 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 (Kessler et al., 2005; Wittchen et al., 2011). PTSD negatively impacts the daily lives of patients and is associated with a higher risk of mortality (Kessler, 2000; Schlenger et al., 2015). Trauma-focused cognitive behavioral therapy (CBT) and eye movement desensitization and reprocessing therapy (EMDR) are among the first choices of treatment (Bisson et al., 2019; Lewis et al., 2020a). Exposure is an important component of CBT and EMDR. During exposure, it is important that memories of the trauma are vividly recalled in order to process them and decrease the PTSD symptoms.

Psychological therapies for PTSD have been found to have a pooled mean dropout rate of 16% (Lewis et al., 2020b). After an evidence-based trauma-focused therapy only 33–56% of PTSD patients no longer meet the criteria for a PTSD diagnosis (Bradley et al., 2005; Steenkamp et al., 2015). Although current therapies are effective, they do not adequately

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help all patients and many patients continue to have symptoms, even if they no longer meet the criteria for the diagnosis (Hoge et al., 2016). Trauma-focused imaginal exposure therapies may not be effective if patients are unable to sufficiently recall the traumatic event and its associated affects. Studies have shown that avoidant coping and poor emotional engagement throughout therapy resulted in poorer treatment outcomes (Badour et al., 2012; Jaycox et al., 1998). In addition, in vivo exposure therapy is not always feasible: it can be impractical to recreate traumatic stimuli in the consultation room or direct surroundings. There is a need for innovations that improve the exposure process in order to increase the efficacy of existing psychotherapies.

An interesting development has been the application of modern technology to increase the efficacy of current PTSD therapies. Augmented reality exposure therapy (ARET) and virtual reality exposure therapy (VRET) are both relatively new types of digitally assisted exposure therapy (Riva et al., 2016). ARET adds digital fear stimuli to the physical world surrounding the user, aided by an interactive digital device such as a computer, smartphone or tablet. Hence, the patient can be exposed to the fear stimulus while still being present in the real world. VRET more fully immerses the patient in digital surroundings; the patient can either see the digital environment on large projection screens (surrounding the patient) or through a motion-sensitive head-mounted visual display system (HMD). The virtual environment depicts fear stimuli created with the use of video, audio and sometimes tangible objects or sensations, such as smells. ARET and VRET aim to increase the sense of presence during exposure therapy, thereby improving the efficacy of the treatment. These treatments are less dependent on the patient's imagination and make it possible to reproduce the traumatic stimuli in a controlled and realistic way. Previous research has found that both ARET and VRET are promising treatments for phobias, such as agoraphobia and arachnophobia (Botella et al., 2017; Chicchi Giglioli et al., 2015).

Although ARET and VRET have existed for more than a decade, they are not recommended as a first-choice psychotherapy for PTSD. This is likely due to the limited body of research currently available that has tested the efficacy of these therapies. To the best of our knowledge, no systematic reviews have studied the efficacy of ARET for the treatment of PTSD. Eight previous systematic reviews on the efficacy of VRET for PTSD found it to be a promising therapy (Botella et al., 2015; Carl et al., 2018; Deng et al., 2019; DiMauro, 2014; Fodor et al., 2018; Kothgassner et al., 2019; Motraghi et al., 2014; Rigoli and Kristensen, 2014). The reviews, however, often did not include a quality assessment or perform an exhaustive inclusion of articles. These reviews frequently included non-controlled trails or articles that failed to compare VRET with a control group that was not treated with VRET. In addition, most reviews did not examine the safety of VRET. Finally, some articles may be dated as VRET technology has been vastly developed in recent years.

This study aims to perform an up-to-date systematic review of current literature regarding the efficacy of ARET and VRET as a PTSD treatment while addressing the limitations of the previous reviews. The information is then synthesized in meta-analyses to present its potential for clinical practice and guide the future research agenda.

2. Methods

This study was carried out in accordance with the PRISMA statement – Preferred Reporting Items for Systematic Reviews and Meta-analyses (Moher et al., 2009).

2.1. Search strategy

This review aimed to identify all the published articles that have studied the efficacy of ARET or VRET as a treatment for PTSD. Search terms for PTSD were combined with search terms for ARET and VRET (see Supplementary Material). A systematic electronic literature search using the databases PubMed, PsycINFO, Medline and PTSDpubs (formerly PILOTS) was conducted on October 23, 2017 and updated on June 29, 2020. The search was not limited by date restrictions but excluded unpublished literature. In addition, we used the references of articles included in our review to search for other relevant publications. Two reviewers (L.E. and M.G.) performed the total search independently and included the articles based on eligibility criteria.

2.2. Eligibility criteria

Studies were included when: 1. The patients had PTSD symptoms or were diagnosed with PTSD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth or Fifth Edition (DSM-IV or −5); 2. ARET and/or VRET were used as a therapy or as a supplement to an evidence-based therapy to reduce PTSD symptoms; 3. The study focused on the efficacy of ARET and/or VRET to reduce PTSD symptoms; 4. PTSD symptoms were assessed with validated PTSD assessment instruments; self-reported or clinician-rated; 5. The study compared a group receiving ARET and/or VRET to a comparison group that did not receive treatment or received another type of treatment; 6. ARET consisted of the use of an interactive device that added digital content to the physical environment surrounding the patient; and 7. VRET minimally consisted of the use of either an HMD that immersed a patient into a digital environment or a large projector screen that displayed the virtual environment. Articles were excluded when trials were: 1. Published in languages other than English or Dutch; 2. Case reports; and 3. Studies without a control group.

2.3. Study selection

Fig. 1 shows an overview of the study search and selection process. The primary search of the electronic databases yielded 1683 results. After excluding duplicates, 1215 articles remained. Exclusion based on title, abstract and eligibility criteria narrowed the articles down to the eleven included in this review. The discrepancies, 32 from the title and abstract search, were discussed and resolved leading to consensus.

2.4. Data extraction

Two assessors (L.E. and M.G.) independently extracted the data from the eleven included articles. Any disagreements were resolved through discussion. The following information was extracted from the articles: study design, amount of randomized and analyzed participants, type of PTSD assessment instrument, type of participants, type of trauma experienced, time since trauma, participant demographic characteristics, type of VR/AR treatment, type of control group treatment, outcome measures, outcomes, adverse events, follow-up, and effect sizes.

2.5. Quality assessment

A systematic quality assessment was performed for each article to determine the quality of reporting and the presence of methodological bias. Two reviewers (L.E. and M.G.) independently assessed the articles. The included articles by van Gelderen et al. (2020) and Bisson et al. (2020) were co-authored by the second author of this review. The quality assessments of these articles were therefore performed by the authors L.E. and A.B. Any disagreements were resolved through discussion. The two critical appraisal tools were the Cochrane Collaboration's Tool for Assessing Risk of Bias in Randomized Trials (Higgins et al., 2011) and the Consolidating Standards of Reporting Trials (CONSORT) 2010 Statement (Schulz et al., 2011) augmented by the 2008 CONSORT Extension for Trails of Nonpharmacologic Treatments (Boutron et al., 2008). Both tools are internationally recognized for assessing the quality of articles (Plint et al., 2006; Zeng et al., 2015). The Cochrane Collaboration's tool was used to appraise selection, detection, attrition, and reporting bias. Every risk of bias was assessed as 'low', 'high' or 'unclear' in each study. The reporting bias appraisal was

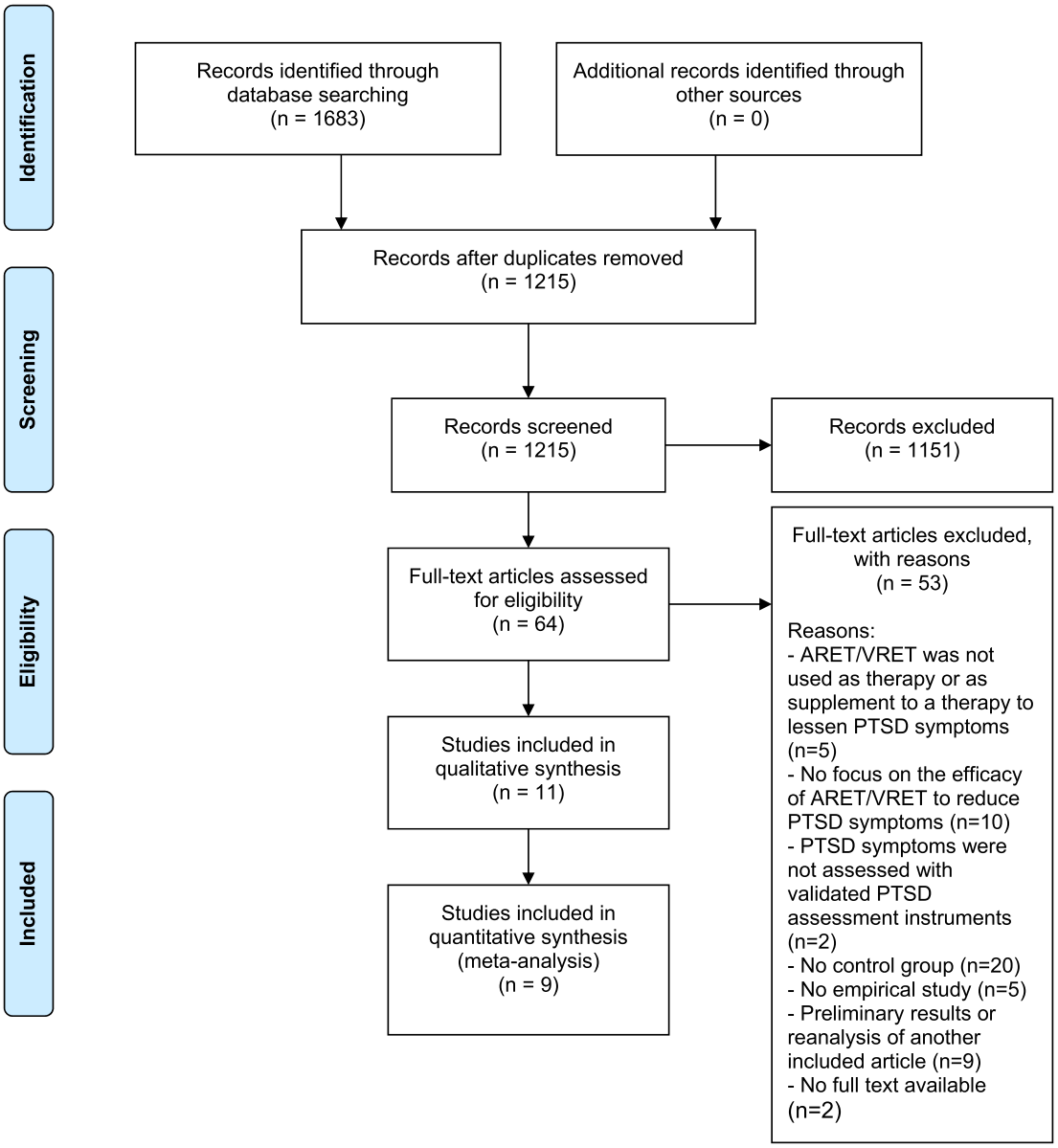

Fig. 1. PRISMA flow diagram for study selection.

carried out by searching for the protocols of the included studies on the websites: https://clinicaltrials.gov, https://www.isrctn.com and https://trialregister.nl. We added the criterion 'Other bias' to assess potential conflicts of interest. The criterion 'Performance bias' was removed as blinding participants and therapists during psychological interventions can be infeasible and unethical (Munder and Barth, 2018). In addition, we studied the reporting of essential information with the CONSORT 2010 checklist and extension. The items were scored with '0' (criteria not met), '1' (criteria partly met), '2' (criteria fully met) or 'X' (criteria did not apply for the article). The full scoring system can be found in the Supplementary Material. One of the included articles reported very little information on the methods used (Miyahira et al., 2012). We could not reach the author to obtain additional information and therefore only used the article's limited information for our quality assessment. The Roy et al. (2014) article was a follow-up to an earlier article by the same author (Roy et al., 2010). The author confirmed the same methods were used in both the 2014 and 2010 studies (personal communication). For this reason, we consulted the methods of both articles for the data-extraction and quality assessment of the 2014 article.

2.6. Calculation of effect sizes

To summarize our results, we executed meta-analyses using Review Manager Software 5.3. We used random effects models for the analyses because of the expected heterogeneity of the studies. Standardized mean differences were applied to measure the effect with 95% confidence intervals (95% CI). The number of participants was extracted from each article using the post-treatment assessment completers. The Clinician-Administered PTSD Scale (CAPS) post-treatment scores and their standard deviations (SD) were extracted from the articles. Pre-treatment CAPS scores were not used, as most studies did not provide the exact scores. However, all the studies reported no significant difference between the mean pre-treatment CAPS scores of their various treatment groups. Forest plots were used to illustrate the results of the meta-analyses. We used I^2 values to assess the heterogeneity of the included studies. Two of the eleven articles did not report post-treatment CAPS scores (Botella et al., 2010; Gamito et al., 2010). The first authors were contacted to obtain this information but there was no reply. These articles were therefore omitted from the meta-analyses.

3. Results

3.1. Study characteristics

All eleven articles studied the efficacy of VRET for the treatment of PTSD. There were no articles identified that studied the efficacy of ARET as treatment for PTSD. Table 1 gives an overview of the study and treatment characteristics of the eleven articles included in this review. More extensive tables with characteristics can be found in the Supplementary Material. The total number of participants analyzed in the eleven studies was 438 (VRET group n = 192, Active treatment control group n = 148, Waitlist control group n = 98). The mean number of participants that were analyzed across the studies was 40 (range 9–162). Ten articles were randomized controlled trials. Difede et al. (2007) adapted a quasi-experimental design that used intact units to assign an experimental group to their participants. The participants that had failed earlier treatment could then be placed in the VRET group.

The majority of the studies included participants who were either active-duty service members or combat veterans (Bisson et al., 2020; Gamito et al., 2010; McLay et al, 2011, 2017; Miyahira et al., 2012; Ready et al., 2010; Reger et al., 2016; Roy et al., 2014; van Gelderen et al., 2020). The study by Botella et al. (2010) included participants suffering from PTSD due to various traumas and Difede et al. (2007) included participants suffering from PTSD after witnessing the Word Trade Center (WTC) attacks on September 11, 2001. The structured CAPS interviews for DSM-IV and DSM-5 were used both as primary outcome measures and to assess the PTSD diagnostic criteria (Weathers et al., 2018). The CAPS cut-off scores for DSM-IV ranged from 40 to 65 points for a PTSD diagnosis, however three articles did not report cut-off scores (Botella et al., 2010; Difede et al., 2007; Gamito et al., 2010). The cut-off scores for CAPS-5 are unavailable. There was only one study that did not report on whether the participants with PTSD symptoms had been formally diagnosed with the disorder (Miyahira et al., 2012). Two articles did not report participant demographic characteristics (Miyahira et al., 2012; Roy et al., 2014). The mean age within the articles ranged from 28 to 64 years old. With the exception of one article (Botella et al., 2010), most studies had a high percentage of male participants (88–100%).

3.1.1. Treatment characteristics

In the majority of the intervention groups VRET was used during the exposure part of the therapy and the groups also received other types of psychotherapy, such as trauma-focused CBT. Van Gelderen et al. (2020) and Bisson et al. (2020) used a type of therapy called 3MDR

Table 1
Study and treatment characteristics.

Author	Participants (n)	VR treatment	Control group(s)	Treatment sessions (both active and control, if relevant)
Bisson et al. (2020)	42	3MDR (VRET + EMDR + walking on a treadmill)	Waitlist control (received 3MDR with a delay of 12 weeks)	Number of sessions: 2 preparation sessions + 6 3MDR + 1 concluding session Frequency: once a week/Duration: average 63.3 min/Exposure duration: NR
Botella et al. (2010)	10	VRET + CBT	PE + CBT (cognitive restructuring, psychoeducation, breathing training, in vivo exposure and imaginal exposure)	Number of sessions: 9 (if needed an extra 3) Frequency: once a week/Duration: 90 min/Exposure duration: NR
Difede et al. (2007)	18	VRET + CBT	Waitlist control	Number of sessions: not clearly reported, max. 14 sessions (range 6–13) Frequency: once a week/Duration: 75 min/Exposure duration: 45 min
Gamito et al. (2010)	9	VRET + trauma-focused therapy based on cognitive desensitization	Group 1: Imaginal exposure therapy Group 2: Waitlist control	Number of sessions: 12 exposure + 1 psychoeducation Frequency: NR/Duration: NR/Exposure duration: NR
van Gelderen et al. (2020)	43	3MDR (VRET + EMDR + walking on a treadmill) + TAU (incl. medication, if stable for 4 weeks before entering the trial)	Non-specific treatment component control group (NTCC): treatment without trauma-focused elements (including medication and CBT without trauma-focused elements)	Number of sessions: 6 3MDR, if needed an extra 10 TAU, NTCC variable up to 16 weeks[a] Frequency: 3MDR once a week, TAU variable, NTCC variable/Duration: 3MDR 70–90 min, TAU and NTCC variable[a]/Exposure duration: NR
McLay et al. (2011)	19	VRET + physiological monitoring, skills training, relaxation CD	TAU (including PE, cognitive processing therapy, EMDR, group therapy, medication management, substance rehab, inpatient services)	Number of sessions: 3-38 Frequency: up to twice a week/Duration: NR/Exposure duration: NR
McLay et al. (2017)	85	VRET + psychoeducation, in vivo exposure and 1 imaginal exposure session	Control exposure therapy: similar protocol as used in VRET, instead of an HMD a single non-moving image was viewed on a computer	Number of sessions: 8-12 Frequency: up to twice a week/Duration: 90 min/Exposure duration: NR
Miyahira et al. (2012)	22	VRET + CBT	Waitlist control	Number of sessions: 9 exposure + 1 psychoeducation Frequency: twice a week/Duration: NR/Exposure duration: NR
Ready et al. (2010)	9	VRET + audiocassette recordings of the sessions to listen to daily between sessions	PCT, with the active non-specific elements of individual psychotherapy, however without discussing traumatic events	Number of sessions: 10 Frequency: NR/Duration: 90 min/Exposure duration: NR
Reger et al. (2016)	162	VRET + breathing retraining, cognitive and emotional reprocessing of traumatic material	Group 1: PE Group 2: Waitlist control	Number of sessions: 10 sessions intended, mean 7 sessions Frequency: up to twice a week/Duration: 90–120 min/Exposure duration: 30–45 min
Roy et al. (2014)	19	VRET + CBT	PE + CBT (cognitive restructuring, psychoeducation, breathing training, in vivo exposure and imaginal exposure)	Number of sessions: 12-20 Frequency: NR/Duration: 90 min/Exposure duration: NR

Note. CBT = cognitive behavioral therapy, PE = prolonged exposure therapy, NR = not reported, HMD = head-mounted visual display system, 3MDR = multi-modular motion-assisted memory desensitization and reconsolidation (with VRET component), NTCC = non-specific treatment component control group, TAU = treatment as usual, PTC = present-centered therapy.

[a] No significant difference in number of sessions and hours of therapy between the treatment group and control group.

(multi-modular motion-assisted memory desensitization and reconsolidation), which is a combination of VRET, motion and EMDR. The patients walk on a treadmill towards images related to their trauma displayed on large screens. The virtual environments depicted in the studies were mainly combat environments. Botella et al. (2010) used an adaptive display called EMMA's World. EMMA's World uses 3D objects, music, photos and videos to reflect the patient's trauma. Three studies used large projection screens to display the virtual world (Bisson et al., 2020; Botella et al., 2010; van Gelderen et al., 2020). All the other studies employed an HMD to facilitate VRET. The number of VRET sessions attended by the participants ranged from six to 20. Six studies measured the outcomes at post-treatment and did not describe a follow-up. The control groups are shown in Table 1 and can be divided into active control groups that received another type of psychotherapy and waitlist control groups. Two articles incorporated both types of control groups (Gamito et al., 2010; Reger et al., 2016).

3.2. Quality assessment of the studies

3.2.1. Risk of bias within studies

The overall quality of the articles was low (Figs. 2 and 3). Only three of the eleven articles reported complete random sequence generation

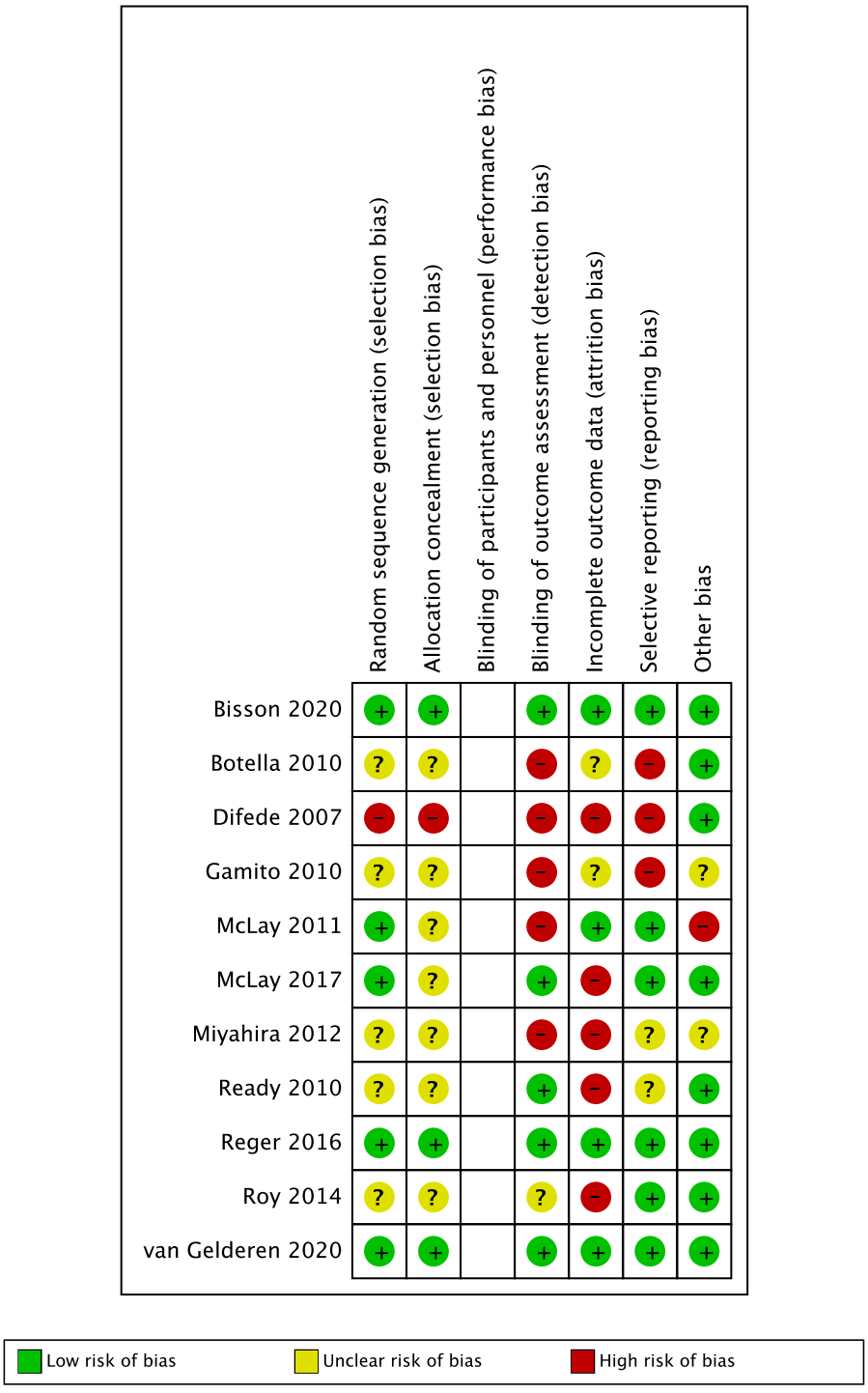

Fig. 2. Risk of bias summary. Note: 'Other bias' is conflicts of interest.

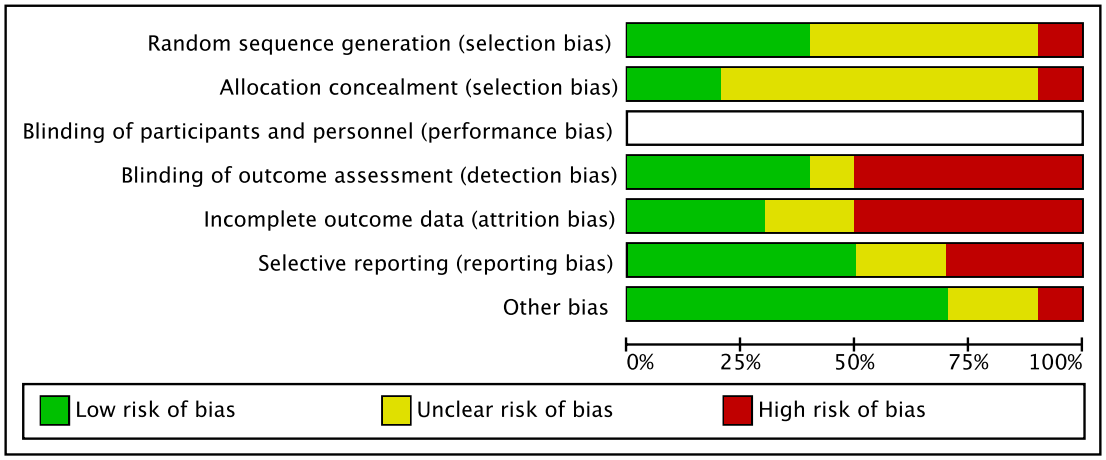

Fig. 3. Risk of bias graph. Note: 'Other bias' is conflicts of interest.

and allocation concealment (Bisson et al., 2020; Reger et al., 2016; van Gelderen et al., 2020). The majority of the articles did not blind the outcome assessment. Furthermore, most of the studies scored a 'high risk' on attrition bias. These articles did not use an intent-to-treat analysis or failed to mention whether participants dropped out of the study. Concerning other biases, three articles reported a potential conflict of interest as they had authors that owned equity in companies that develop virtual reality products for VRET (McLay et al., 2011; Ready et al., 2010; Reger et al., 2016). Two of the articles blinded the outcome assessment and complied with the Emory University conflict-of-interest policies (Ready et al., 2010; Reger et al., 2016), however, the third article did not blind the outcome assessment and therefore scored 'high risk' (McLay et al., 2011).

3.2.2. *Quality of reporting within studies*

The CONSORT checklist for all the included articles is summarized in Figs. 4 and 5. The overall quality of reporting within the studies was poor. Only three articles properly described 50% or more of the required information (Bisson et al., 2020; Reger et al., 2016; van Gelderen et al., 2020). The first author of this current systematic review can be contacted to obtain each article's full CONSORT checklist scoring sheet.

3.3. *Results of individual studies*

There were two types of comparisons used in the designs of the included studies: VRET vs. waitlist control and VRET vs. active control psychotherapy. The reported dropout rate ranged from 0 to 52.4% in the

	Title and abstract	Background and objectives	Trial design	Participants	Interventions	Outcomes	Sample size	Randomization: sequence generator	Allocation concealment mechanism	Implementation	Blinding	Statistical methods	Participant flow	Implementation of intervention	Recruitment	Baseline data	Number analyzed	Outcome and estimation	Ancillary analyses	Harms	Limitations	Generalizability	Interpretation	Registration, protocol, funding
Bisson 2020	+	+	+	+	+/-	+	+	+	+	+	+	+	+	+/-	+/-	+/-	+	+	+	-	+	+	+/-	+/-
Botella 2010	-	-	-	+/-	+/-	+/-	-	-	-	-	-	+/-	-	-	-	-	-	+/-	X	-	+	-	-	-
Difede 2007	+/-	+	+/-	+	+/-	+/-	-	X	X	X	-	+/-	+/-	+/-	+/-	+	+/-	-	+/-	-	+	+/-	+/-	-
Gamito 2010	-	+/-	-	-	-	+/-	-	-	-	-	-	+/-	-	-	-	-	-	-	+/-	-	+/-	-	-	-
McLay 2011	+	+	-	+	+/-	+	-	+/-	+/-	-	-	+/-	+/-	+/-	-	+/-	+/-	+	+/-	+	+	+	+	-
McLay 2017	+	+	+/-	+/-	+	+	+/-	+	-	-	+/-	+/-	+/-	-	-	+/-	+	+/-	+	-	+	+/-	+/-	+/-
Miyahira 2012	-	+/-	-	-	-	+/-	-	-	-	-	-	-	-	-	-	-	+/-	+/-	X	-	+/-	-	-	+/-
Ready 2010	+/-	+	-	+/-	+/-	+/-	-	-	-	-	+/-	+/-	+/-	-	-	-	+	+/-	+	-	+/-	-	+/-	-
Reger 2016	+	+	+	+/-	+	+	+/-	+	+	+	+	+/-	+/-	+	+	+	+	+	+	+	+	+	+	+/-
Roy 2014	-	+/-	-	+/-	+/-	+	-	-	-	-	-	-	+/-	-	-	-	-	+/-	X	-	+/-	-	-	-
van Gelderen 2020	+	+	+	+	+	+	+/-	+	+	+/-	+	+	+	+	+	+/-	+	+	+	+	+	+	+	+/-

+ Item fully met
X Item does not apply
- Item not met
+/- Item partly met

Fig. 4. Quality of reporting summary.

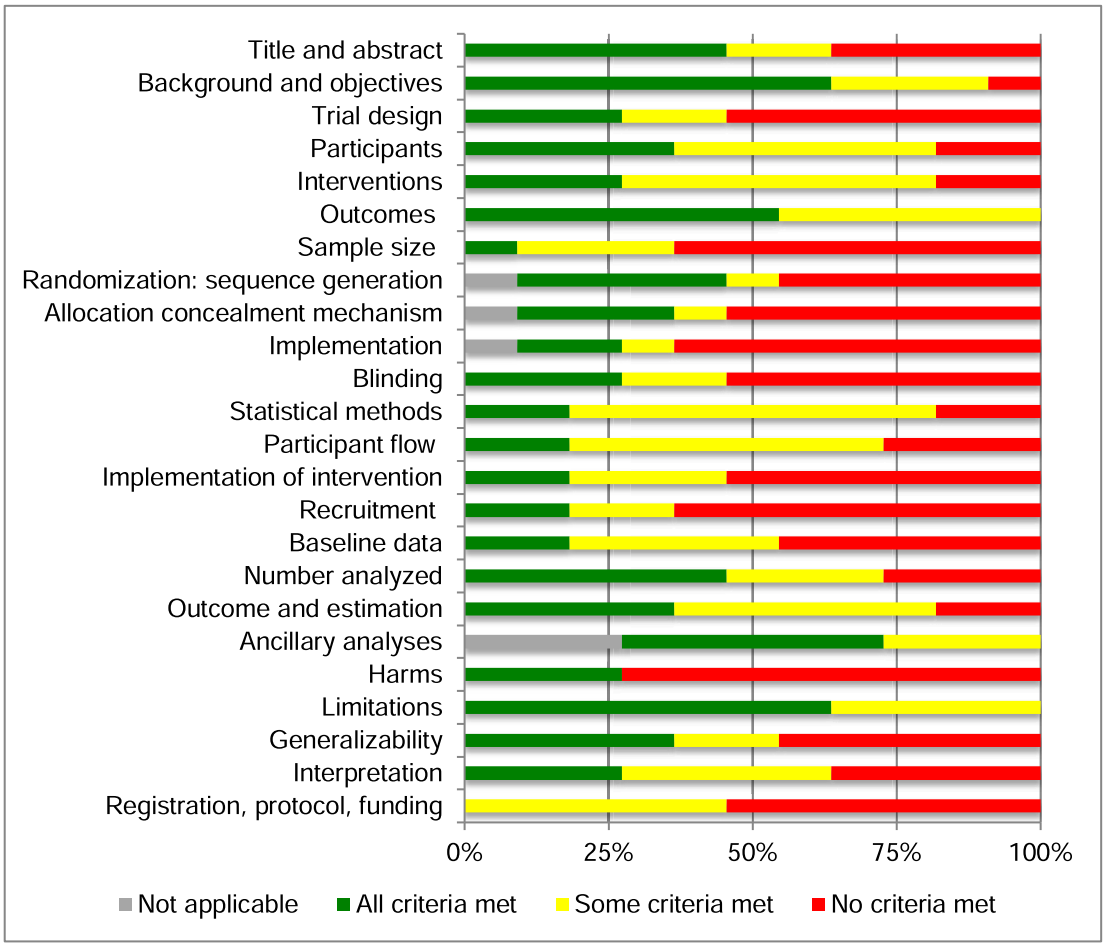

Fig. 5. Quality of reporting graph.

period from pre- to post-assessment, with a pooled mean dropout rate of 21.9%. The study results are summarized in Table 2. There was a substantial level of heterogeneity between the different studies with eight of the eleven studies reporting a significant decrease in the VRET group CAPS score, two of the eleven studies reporting significantly decreased CAPS scores in control conditions, and five of the eleven studies reporting a significant difference between the treatment groups. Two articles reported that there had been no occurrence of adverse events (McLay et al., 2011; van Gelderen et al., 2020) and a third article stated that a worsening of PTSD symptoms was rare (<3.5%) (Reger et al., 2016). One article did not systematically report adverse events or side effects but wrote that patients did not feel overwhelmed by VRET and there were no patients whose PTSD symptoms had worsened (Difede et al., 2007). The other seven included articles did not report on adverse events and side effects.

3.4. *Quantitative synthesis of results*

Two separate meta-analyses were carried out. The first analysis compared VRET with a waitlist control group and the second analysis compared VRET with other active psychotherapies. The article by Reger et al. (2016) was included in both meta-analyses.

The meta-analysis comparing VRET with a waitlist control group showed that patients in the VRET group had a significantly larger decrease in PTSD symptoms than patients in the waitlist control group, with a standardized mean difference at post-treatment of −0.64 (95% CI -1.05 to −0.22) (Fig. 6). The meta-analysis comparing VRET to active control therapies showed there was no significant difference in efficacy between VRET and active controls, with a standardized mean difference at post-treatment of −0.25 (95% CI -0.77 to 0.27) (Fig. 6). The I^2 values were respectively 26% and 69% and represent a low to substantial heterogeneity between the studies.

4. Discussion

This systematic review and meta-analysis set out to investigate the efficacy of ARET and VRET as treatments for PTSD and to compare its efficacy to other types of active PTSD therapy. Unfortunately, no articles were found that studied ARET as a treatment for PTSD. A total of eleven VRET studies were included, of which ten studies were randomized controlled trials. The meta-analyses demonstrated that the efficacy of VRET was significantly greater than waitlist control and was as effective as other active psychotherapies. Generally, earlier reviews showed that VRET could possibly be an effective treatment for PTSD though it did not seem superior to other trauma-focused treatments (Deng et al., 2019; Freeman et al., 2017; Kothgassner et al., 2019; Maples-Keller et al., 2017). Our meta-analyses confirmed these findings and furthermore included the most recent studies on this subject.

These results should, however, be interpreted with caution, as the studies comparing VRET to waitlist or active control groups showed substantial heterogeneous results in the qualitative synthesis of the data. This is in line with previous reviews on this topic (Fodor et al., 2018; Motraghi et al., 2014; Rigoli and Kristensen, 2014). These varying results may be caused by the overall low quality of the studies or the differing treatment protocols. Yet the quality of studies on this subject seems to be improving. The most recent articles included in this review had larger numbers of participants, a relatively good quality of reporting and a low risk of bias (Bisson et al., 2020; McLay et al., 2017; Reger

Table 2
Outcomes of individual studies.

Author	Dropout	Significantly decreased CAPS score in VRET group at post-treatment (PT) and follow-up (FU)	Significantly decreased CAPS score in control group at post-treatment (PT) and follow-up (FU)	Significant CAPS difference between treatment groups at post-treatment[a] (and follow-up)
VRET vs. Waitlist control				
Bisson et al. (2020)	31%[b] (61.5% in VRET group)	PT: YES FU: NR	PT: NR (WL) FU: NR[c]	PT: YES (Waitlist CAPS scores > VRET CAPS scores) FU: NO[c]
Difede et al. (2007)	14% (allin VRET group)	PT: YES FU: YES at 6 months	PT: NO (WL) FU: NO	PT and FU: YES (Waitlist CAPS scores > VRET CAPS scores)
Gamito et al. (2010) (a)	10% (all in VRET group)	PT: NO	PT: NO (WL)	PT: NO
Miyahira et al. (2012)	52.4% (65.5% in VRET group)	PT: NO	PT: NO (WL)	PT: NO
Reger et al. (2016) (a)	32.7% (VRET: 44.4%, PE: 40.7%, WL: 13.0%)	PT: YES FU: YES at 6 months	PT: NO (WL) FU: NO	PT and FU: YES (Waitlist CAPS scores > VRET CAPS scores)
VRET vs. Active control				
Botella et al. (2010)	NR	PT: YES	PT: NO (PE + CBT)	PT: NO
Gamito et al. (2010) (b)	See Gamito (a)	PT: NO	PT: NO (IE)	PT: NO
van Gelderen et al. (2020)	7% (3MDR: 66.7%, NTCC: 33.3%)	PT: YES	PT: NO (NTCC)	PT: YES (NTCC CAPS scores > VRET CAPS scores)
McLay et al. (2011)	5% (all in TAU group)	PT: NR	PT: NR (TAU)	PT: NO
McLay et al. (2017)	8.6% (all in VRET group)	PT: YES FU: YES at 3 months	PT: YES (CET) FU: YES	PT and FU: NO
Ready et al. (2010)	18% (VRET: 50%, PCT: 50%)	PT: NO FU: NO at 6 months	PT: NO (PCT) FU: NO	PT and FU: NO
Reger et al. (2016) (b)	See Reger (a)	PT: YES FU: YES at 6 months	PT: YES (PE) FU: YES	PT: NO FU: YES (VRET CAPS scores > PE CAPS scores)
Roy et al. (2014)	0%	PT: YES	PT: NO (PE + CBT)	PT: NR

Note. NR = not reported, WL = waitlist control, IE = imaginal exposure therapy, 3MDR = multi-modular motion-assisted memory desensitization and reconsolidation, NTCC = non-specific treatment component control, PE = prolonged exposure therapy, CET = control exposure therapy, TAU = treatment as usual, CBT = cognitive behavioral therapy.

[a] Waitlist CAPS scores > VRET CAPS scores indicates a positive effect of VRET.

[b] Four participants completed therapy early and were therefore not included in the dropout rate.

[c] At follow-up the waitlist control group had also received 3MDR in the cross-over study design.

et al., 2016; van Gelderen et al., 2020). There is an argument that more weight should be attributed to the outcomes of these recent studies. They presented the use of VRET as being more effective than the waitlist control condition and comparable to or more effective than active control conditions. We can cautiously state that the evidence for the efficacy of VRET is getting stronger.

Besides studying the efficacy of VRET, it is also crucial to study the safety of the treatment. The lack of reporting on side effects and adverse events in psychotherapy is a long-standing problem (Berk and Parker, 2009; Linden, 2013). A possible reason for this is that there is no consensus on a classification system for adverse events and side effects in psychotherapy (Linden, 2013). Furthermore therapists, in order to protect themselves, may not always report adverse events that are caused by their own actions (Linden, 2013). This lack of reporting in psychological trials is concerning as earlier research has shown that a large number of patients report experiencing negative effects during or after psychotherapy (Ladwig et al., 2014). Exposure therapy in general can lead to adverse events such as exacerbations of PTSD symptoms (Hendriks et al., 2018). This effect may be stronger for VRET, as it can be a particularly realistic form of exposure therapy and may therefore arouse more anxiety, anger or stress than other types of exposure therapy. Yet only three of the eleven studies that were included in this review systematically reported side effects and adverse events. These three studies presented VRET as a safe treatment, reporting there was no occurrence of adverse events and a worsening of PTSD symptoms was rare (<3.5%) (McLay et al., 2011; Reger et al., 2016; van Gelderen et al., 2020). One additional study did not systematically report adverse events but reported that none of the patients experienced a worsening of PTSD symptoms (Difede et al., 2007). Although there is a limited amount of knowledge on the safety of VRET, it is crucial that the exposure therapy takes place in a safe environment (Goode et al., 2015). Most of the included studies reported delivering VRET in a gradual manner, increasing the intensity of the exposure sessions over time (Difede et al., 2007; Gamito et al., 2010; McLay et al, 2011, 2017; Ready et al., 2010; Reger et al., 2016; Roy et al., 2014). In addition, three of the included studies used photographs and symbolic stimuli during the exposure therapy instead of fully immersing the patient in the virtual environment (Bisson et al., 2020; Botella et al., 2010; van Gelderen et al., 2020). These methods may be a step towards protecting the participant from an overwhelming exposure experience. Research has demonstrated that distress during VRET was not significantly higher than that experienced during prolonged exposure therapy (Reger et al., 2019). To draw firm conclusions, further systematic research into the safety of VRET is important and necessary. There should be a use of models that systematically classify and assess psychotherapy side effects (Ladwig et al., 2014; Linden, 2013).

We need to have a more complete picture of the benefits and risks of VRET as it has the potential to be more effective than traditional psychotherapies in specific patient populations. It may optimize the emotional engagement for treatment-resistant patients that, for example, cannot immerse themselves sufficiently in standard imaginal exposure therapy. PTSD patients have reported a high degree of immersion when VRET is applied and studies show that increased emotional engagement can improve treatment outcomes (Cooper et al.,

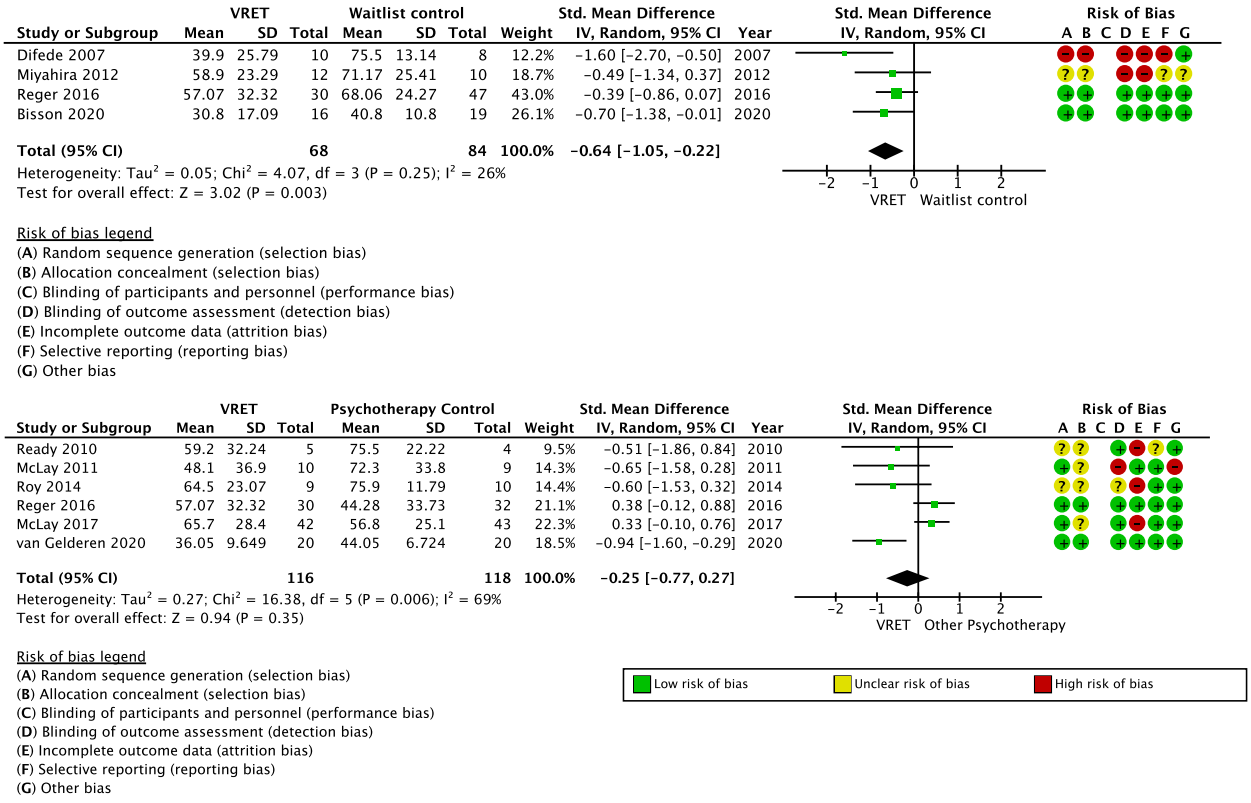

Fig. 6. Forest plots of meta-analyses VRET vs. Waitlist control and VRET vs. Active control therapies.

2017; Kramer et al., 2013). Four studies in this current review featured a VRET group that included psychotherapy resistant patients because previous PTSD treatments had failed (Bisson et al., 2020; Difede et al., 2007; McLay et al., 2011; van Gelderen et al., 2020). The studies found that VRET was more effective than waitlist control and just as effective or more effective than active control therapies. The most recent studies showed that 3MDR (VRET + walking on a treadmill + dual-attention task) was more effective than waitlist control and more effective than psychotherapy without trauma-focused elements (Bisson et al., 2020; van Gelderen et al., 2020). The authors hypothesize that the process of literally walking towards the feared virtual stimuli may stimulate fear extinction and associative thinking, which could heighten the efficacy of the therapy. Furthermore, VRET, with its use of digital media, could potentially be less stigmatizing than other forms of psychotherapy, leading to fewer dropouts. Yet the pooled mean dropout rate of the reviewed studies was higher than the mean dropout rate of traditional psychotherapies (21.9% vs. 16%) (Lewis et al., 2020b). However, the dropout rates of three of the studies on treatment-resistant patients were lower than 16% (respectively 14%, 5% and 7%) (Difede et al., 2007; McLay et al., 2011; van Gelderen et al., 2020). VRET may attract patients that are reluctant to take medicine or to receive traditional talking therapy. Previous research among American soldiers found that 33% of the participants that were not willing to talk to a counselor in person, were, however, willing to use technology-based therapy (Wilson et al., 2008).

One of the strengths of this review is that it addressed the limitations of previous reviews and it only included studies that compared VRET with a control group that did not receive VRET. This review thoroughly assessed the quality of the design and reporting of each of the studies. Two independent assessors carried out the full search, the data-extraction and the quality assessment. Furthermore, this is the first review that systematically searched for articles that studied the efficacy of ARET for PTSD. One of the limitations of this review was that we were unable to directly compare specific forms of trauma-focused psychotherapy to VRET in the meta-analyses due to the limited number of existing articles. Secondly, we were unable to use pre-treatment CAPS scores in the meta-analyses as these scores were rarely described in the included articles. However, this is unlikely to have influenced the results of the analyses because all the articles reported no significant difference in pre-treatment CAPS scores between treatment groups. Thirdly, there is a risk of performance bias in RCTs with psychological treatments as it is often not possible to blind patients and therapists to the intervention they are receiving or administering. We have to be vigilant about recognizing this risk when interpreting the studies' results. The studies in this review that used an active comparator could have a lower risk than the studies that used a waitlist control group. Finally, most studies were carried out in the U.S.A., they studied active duty soldiers or veterans and the majority of the participants were men. This means that further research in more diverse populations is warranted for broader generalizability.

In terms of clinical implications, it is important to pose the question - is the non-inferiority of VRET compared to other (exposure-based) psychotherapies sufficient enough to implement VRET in clinical practice considering, among other factors, the hardware and software costs? Fortunately, we are seeing an increase in accessibility of software for both VRET and ARET and a decrease in the price of VRET devices with the growth of the VR commercial consumer market (Mishkind et al., 2017). It has even been suggested that VRET may be more cost-effective than treatment as usual (Wood et al., 2009), however well-designed cost-effectiveness studies are still needed to verify this. In addition, specific patient populations, for example treatment-resistant patients, may experience more benefit from VRET. Although VRET does not outperform current evidence-based psychotherapies in our meta-analyses, VRET could become a treatment modality that could be offered to people with PTSD that may benefit from this therapy. When more research is done on the side effects and adverse events of the treatment and the therapist deems the therapy suitable, a patient could make an informed choice to undergo VRET. Zoellner et al. (2009)

suggest that if patients have a range of therapies to choose from and are able to select the therapy they prefer, the engagement and effect of the treatment may improve. Earlier research has shown that PTSD patients that received an undesired treatment, had worse outcomes than patients without opinions about their treatment (Markowitz et al., 2016). Research into veterans' reasons for dropping out of therapy has shown that a lack of buy-in to treatment rational was one of the largest therapy related barriers (Hundt et al., 2018). Treatment for PTSD requires innovative approaches to increase treatment fit (Hoge, 2011). Providing VRET as a treatment option may contribute to this goal.

We recommend that future research examines whether VRET improves immersion during therapy, thereby enhancing emotional engagement and treatment outcome. Further research should be done to determine whether VRET is particularly effective for treatment-resistant PTSD patients. In addition, studies should focus on finding the optimal treatment protocol, possibly by integrating VRET and other treatment elements and by comparing VRET hard- and software. Techniques such as the multiphase optimization strategy (MOST) could be useful for these analyses (Collins, 2018). Finally, it is crucial that future research into VRET should always study and report side effects and adverse events (Guidi et al., 2018).

This study recognizes a research gap regarding the efficacy of ARET in the treatment of PTSD. This may be because research into ARET is in a relatively early stage and, as yet, studies have focused on other disorders. Studies have, for example, indicated that ARET may be beneficial for patients suffering from anxiety disorders (Chicchi Giglioli et al., 2015). We suggest that ARET has the potential to be an effective treatment for PTSD, and in some cases may be more suitable than VRET. ARET differs from VRET in that it provides the possibility of adding traumatic stimuli into the actual environment of the patient. ARET also enables patients to see their own body, instead of the digital body that is often used in VRET. This may result in increased levels of presence. Also, the patient's actual surroundings are augmented when using ARET, while the VRET environment has to be fully designed. This means the idiosyncrasy of highly personalized environments is limited when using VRET while the design process may be more expensive (Baus and Bouchard, 2014; Kramer et al., 2013). A limitation of ARET, however, is that in some cases, for example while treating military soldiers for war-related trauma's, adding stimuli from a warzone to a patient's surroundings could be undesirable. In these cases, VRET may be the first choice, as it can fully immerse patients in a virtual environment. ARET and VRET could potentially be combined during therapy, for example by using VRET in place of imaginal exposure therapy and improving in vivo exposure therapy with ARET. Future research should identify whether ARET is an effective treatment for PTSD, whether it could be even more effective and less costly than VRET and whether combinations of VRET and ARET could heighten the efficacy of PTSD treatment.

This systematic review and meta-analysis showed that VRET as a PTSD treatment outperformed waitlist control groups and was equally effective as other (trauma-focused) psychotherapies. The efficacy of ARET for PTSD could not be studied, as there were no research articles published on this topic. The use of ARET and VRET could lower the stigma surrounding PTSD therapy and increase a patient's sense of presence during exposure therapy. Further research is warranted to study whether VRET can heighten the efficacy of PTSD treatments in certain patient populations.

5. Contributors

Authors L.V. Eshuis, M.J. van Gelderen and A. Bakker designed the study. Authors L.V. Eshuis and M.J. van Gelderen conducted the literature searches and provided summaries of previous research studies. A. Bakker gave advice on these processes. Authors L.V. Eshuis, M.J. van Gelderen and A. Bakker assessed the quality of previous research studies and conducted the statistical analysis. Author L.V. Eshuis wrote the first draft of the manuscript. Authors L.V. Eshuis, M.J. van Gelderen, M. van Zuiden, M.J. Nijdam, E. Vermetten, M. Olff and A. Bakker contributed to the final manuscript. All approved the final manuscript.

Declaration of competing interest

All authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2020.11.030.

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