Joonas Hannula

What is the efficacy of virtual reality exposure therapy in reducing PTSD symptoms?

Systematic review

Faculty of education and psychology

Psychology bachelor's degree programme

2024

10.6.2024

University of Oulu
Faculty of Education and Psychology
What is the efficacy of virtual reality exposure therapy in reducing PTSD symptoms (Joonas Hannula)
Bachelor thesis, 27 pages
June 2024

Abstract

What is the efficacy of virtual reality exposure therapy in reducing PTSD symptoms?

The aim of this systematic review is to explore the effectiveness of a new novel PTSD intervention (virtual reality exposure therapy, VRET) on PTSD symptoms. In this review PTSD symptoms were looked through the scope of the clinician administered PTSD scale (CAPS). Secondary outcome measures that were analyzed were physiological response, depression symptoms and drop-out rates.

This systematic review gathered articles from multiple databases with the main inclusion criteria being, that the study had to report relevant information on the effectiveness of VRET on a sample of clinically significant PTSD participants according to the DSM-IV or DSM-5 classification of PTSD. The assessment of PTSD symptoms had to be done using the clinician administered PTSD scale. The final selection yielded 14 studies.

This review found that VRET reduces CAPS scores significantly and that in follow-up measurements these results are maintained. However, when VRET was compared to other forms of PTSD treatment VRET did not consistently outperform these interventions. In terms of secondary measures, VRET reduced depression symptoms significantly in posttreatment and follow-up measures. Pooled drop-out rate of participants in VRET interventions were markedly higher when compared to relevant literature around PTSD treatment drop-out rates.

In conclusion, VRET in the light of this review looks to be an efficacious form of PTSD treatment in terms of outcome measures such as PTSD symptoms but also secondary measures such as comorbid depression symptoms. However, this claim is hindered by major limitations in population validity and increased drop-out rates when compared to other efficacious treatment forms of PTSD. These limitations have a limiting effect on the generalizability of VRET as an PTSD intervention.

Keywords: posttraumatic stress disorder, virtual reality, exposure therapy, VRET

Contents

1 Introduction

1.1 Posttraumatic stress disorder (PTSD)

The aim of this systematic review is to assess the efficacy of virtual reality exposure therapy (VRET) in treating posttraumatic stress disorder (PTSD) symptoms. More specifically the effect of VRET in reducing PTSD symptoms in clinically affected individuals.

PTSD is categorized in the DSM-5 as a trauma- and stressor-related disorder with the main etiological factor being exposed to actual or threatened death, injury, or sexual violence (Black et al., 2014). In a recent review of world mental health surveys across high-, medium- and low-income countries it was concluded that 54-73.8% of people experience lifetime traumas and of those people 3.5-2.5% develop PTSD (Atwoli et al., 2015). Therefore, there should be great interest in finding efficacious treatment forms for a disorder affecting people on a global scale.

A large-scale etiological review found that most common risk factors for developing PTSD were presence of previous traumatic experiences, psychopathology of both the individual and close family, age concerning very young and very old individuals and gender concerning higher risk for females. The characteristics of the traumatic experience such as severity of perceived danger or death and dissociation were related to developing PTSD. In terms of protective factors perceived social support yielded strongest effect sizes (Keane et al., 2006). In a review of PTSD comorbidity with other disorders in the United States found that 44 % of women and 59 % of men diagnosed with PTSD meet three or more diagnostic criteria for other disorders. In the sample 49 % of women and 48 % of men met the criteria for major depressive disorder (MDD). Other most common comorbid disorders were anxiety disorders and substance use disorders (Kessler et al., 1995).

In the transition from the diagnostic and statistical manual of mental disorders (DSM) fourth edition to the fifth PTSD was one of many disorders that have been transferred from anxiety disorders diagnostic class to its own trauma- and stressor-related grouping (Black et al., 2014). Main symptoms of PTSD in the DSM-5 include the presence of a traumatic event (Criterion A: directly experienced or witnessed), intrusive symptoms (Criterion B: for instance dissociative reactions and involuntary distressing memories), either persistent avoidance of cues relating to

the memory or negative alterations in mood (Criterion C) and altered mood relating to the traumatic event (Criterion D for instance problems concentrating or sleeping and hypervigilance) (Black et al., 2014).

A key difference between the fourth and fifth edition is that criterion A2 has been removed. This criterion stipulated that the person experiencing the traumatic event must have a subjectively distressful reaction at the time of the traumatic event (Black et al., 2014). In a review of the revisions done to the PTSD diagnostic criteria concluded that the predictive validity of this criterion in diagnosing and predicting who develops PTSD was low and was thus excluded in the fifth edition (Black et al., 2014; Friedman et al., 2011).

Another significant difference between the two editions is the separation of the avoidance and numbing symptom cluster into two separate clusters avoidance (criterion-C) and negative alterations in cognition and mood (criterion- D). With the latter seeing change between the editions with only three of the previous seven symptoms being carried over to the DSM-V as these symptoms were seen as overlapping too much with depressive symptoms found in other disorder classifications (Friedman et al., 2011; Weathers et al., 2014). Another noteworthy change between the editions is that the DSM-5 criteria now includes a dissociative symptom subtype. In multiple reviews it has been found that dissociative symptoms have 12-30 % prevalence in PTSD populations and that the presence of dissociative symptoms has a strong association with PTSD symptom severity (Carlson et al., 2012; Lanius et al., 2012).

1.2 Exposure therapy as a framework for VRET

The key theoretical framework for exposure therapies such as VRET is emotional processing theory. This theory was advanced by Foa and Kozak in their 1986 paper in which they combined aspects of previous work on the use of fear imagery to modify fear memory structure (Lang, 1977) and the concept of emotional processing (Rachman, 1980).

Foa and Kozak proposed that to change fear structure that is present in PTSD there needs to be repeated exposure to fear-related stimuli to give access to the fear structure. Then when the feared memory is re-experienced in a safe environment this creates a disconnect between the original cognitive-affective structure and the newly learned structure. These inconsistencies are thus said to reduce the amount of fear and anxiety experienced during exposure to fear-related

stimulus. They also highlighted the importance of the meaning given for these disconnects between old and new responses in fear-related situations in relation to potential successful therapeutic outcomes (Foa & Kozak, 1986). In addition, they emphasize that the fear-related stimulus should be experienced in a safe manner and environment to create the previously mentioned disconnect in the fear structure and therapeutic situation while still maintaining the emotional engagement with the memory. In other words, the habituation happening when re-experiencing the feared situation is important, however this needs to happen in a safe therapeutic environment where the experiences can be explored further and additional tools for coping can be delivered (Foa & Kozak 1986).

Later the theory was elaborated on by highlighting the aspect of emotional engagement during exposure in treatment outcomes (Foa & Hearst-Ikeda, 1996). They suggest that in exposure therapy some people might have difficulties in engaging emotionally with their traumatic memories as avoidance and numbing symptoms are very common in PTSD. They linked the lack of emotional engagement to the link between PTSD symptom severity and dissociation symptoms (Foa & Hearst-Ikeda, 1996). As mentioned earlier, this link is supported by a review that concluded that there is a strong link between dissociation symptoms and PTSD symptom severity (Carlson et al., 2012). This aspect of emotional engagement has been hypothesized to be better achieved by VRET than conventional methods of image or audio exposure as it immerses the person more than traditional exposure therapy methods (Kothgassner et al., 2019).

An important distinction to be made is that both PE and VRET are trauma-focused therapy forms. However, the treatment of PTSD can also be non-trauma focused, usually in the forms of traditional psychotherapy such as cognitive behavioral therapy or present-centered therapy(Lewis et al., 2020).

1.3 VRET

The area of research regarding the use of technology such as virtual reality in psychological interventions is relatively new: this coincides with the emergence and lessened cost of VR equipment. These factors bring forth the opportunity of constructing virtual reality-based personalized therapeutic and psychological assessment environments which can be a great resource moving forward.

As mentioned earlier this development in VR technology has been theorized to have its uses in exposure therapy. The virtual reality environment could improve the ecological validity regarding exposure stimulus which has been regarded as the key aspect of exposure therapy's emotional processing theory framework. This is because VRET can deliver virtual reality-based fear-related stimulus whereas the traditional form relies on physical images or imaginative methods as stimulus (Rothbaum & Hodges, 1999). For instance, traditional prolonged exposure therapy uses imagining techniques such as the therapist asking the participant to recount the traumatic events out loud while having their eyes closed. Traditional exposure therapies also use in vivo exposure such as physical images, smells and sounds in conjunction to the previously mentioned recounting exercises (Lewis et al., 2020). In contrast to this VRET uses virtual reality headsets and other equipment to deliver an audiovisual virtual reality environment that encompasses the full visual field of the individual. The virtual reality environment is linked to the participants traumatic memory and the same technique of recounting the traumatic event out loud to the therapist is commonplace. Furthermore, the virtual reality environment is responsive to participant action allowing the participant to move in the three-dimensional space (Rothbaum & Hodges, 1999).

However, the possibility of these improvements should be approached cautiously as trauma focused treatment forms of PTSD like prolonged exposure therapy have a relatively high drop-out rates compared to other PTSD treatment forms (Lewis et al., 2020). Thus, experiencing trauma-related stressors in an immersive virtual reality constructed environment can be overwhelming and should be approached carefully. In contrast, regarding the drop-out rates from exposure therapies some have theorized that it might be the lack of possible emotional engagement with the stimulus which causes the high drop-out rates and frustration with traditional exposure therapies. Hence the implementation of virtual reality could prove efficacious to solving this issue. (Deng et al., 2019). It has been hypothesized that for instance the immersive field of view using the VR-headset might deny the opportunity to use avoidance tactics in the face of encountering traumatic memories and thus improve emotional engagement during treatment sessions. (Deng et al., 2019).

Earlier studies have shown promising results in regard to the effect of VRET on PTSD but with relatively small sample sizes (Difede et al., 2007; Ready et al., 2010). Newer studies have included larger sample sizes (Beidel et al., 2017, 2019; Difede et al., 2022; McLay et al., 2017; Reger et al., 2016; Rothbaum et al., 2014). Therefore, it will be important for the future of

VRET to see if it can show similar results consistently in larger samples and randomized controlled trial settings. Additionally, in a recently published meta-analysis of VRET outcomes in anxiety disorders found that VRET had strong pooled effect sizes for treating both specific phobias and social anxiety (g = 0.95 & g = 0.97 respectively) (Carl et al., 2019). It will be important to see similar results can be established for the treatment of PTSD symptoms.

1.4 Clinician administered PTSD scale (CAPS)

To assess the efficacy of VRET in reducing PTSD symptoms this review will review PTSD symptoms through the clinician administered PTSD scale (CAPS). CAPS was by far the most common assessment tool of PTSD symptoms in the reviewed literature. This similarity between studies creates a good degree of comparability between different study-designs and samples.

The CAPS fourth edition is a structured interview that is performed by a clinician to assess the frequency and severity of the 17 DSM-IV PTSD symptoms. The total severity scores on fourth edition of the CAPS range from 0-136. On the CAPS-IV a score larger than 40 on the interview has been deemed clinically significant for the presence of PTSD symptoms (Weathers et al., 2001). This is supported by empirical evidence as in a study that predicted PTSD development in a trauma population found that CAPS administration one month after the traumatic event predicted PTSD development at four months. Furthermore, the study presented a cutoff score of 40 points on the CAPS-IV that resulted in 0.93 sensitivity and 0.80 specificity (Shalev et al., 1997).

The greatest difference in terms of outcome measures in the selected studies was whether it used the 4th or 5th edition of the scale. The changes between the CAPS editions are reflected by the aforementioned changes in the DSM-IV and DSM-5 PTSD criterion (Weathers et al., 2018). The key changes seen in the CAPS structure were: As mentioned, the DSM-IV criterion A2 was removed, thus questions on the CAPS regarding the criterion A2 symptoms were removed and DSM-5 increased the symptom cluster by separating avoidance and numbing clusters so those were also separated in the CAPS-5 with separate questions (Weathers et al., 2018)

Another significant change between the two editions is on how the different items are scored. The newer fifth edition is a 30-item structured interview with severity scores ranging from 0-

80 compared to the 0-136 range on the CAPS-IV. In the same vein the CAPS-5 assesses the DSM-5 PTSD symptoms in both frequency and severity (Weathers et al., 2018).

2 Method

The method used in this literature review was that of a systematic review of the available literature. The following section will report on the study selection process and participant and study characteristics.

2.1 Selection process

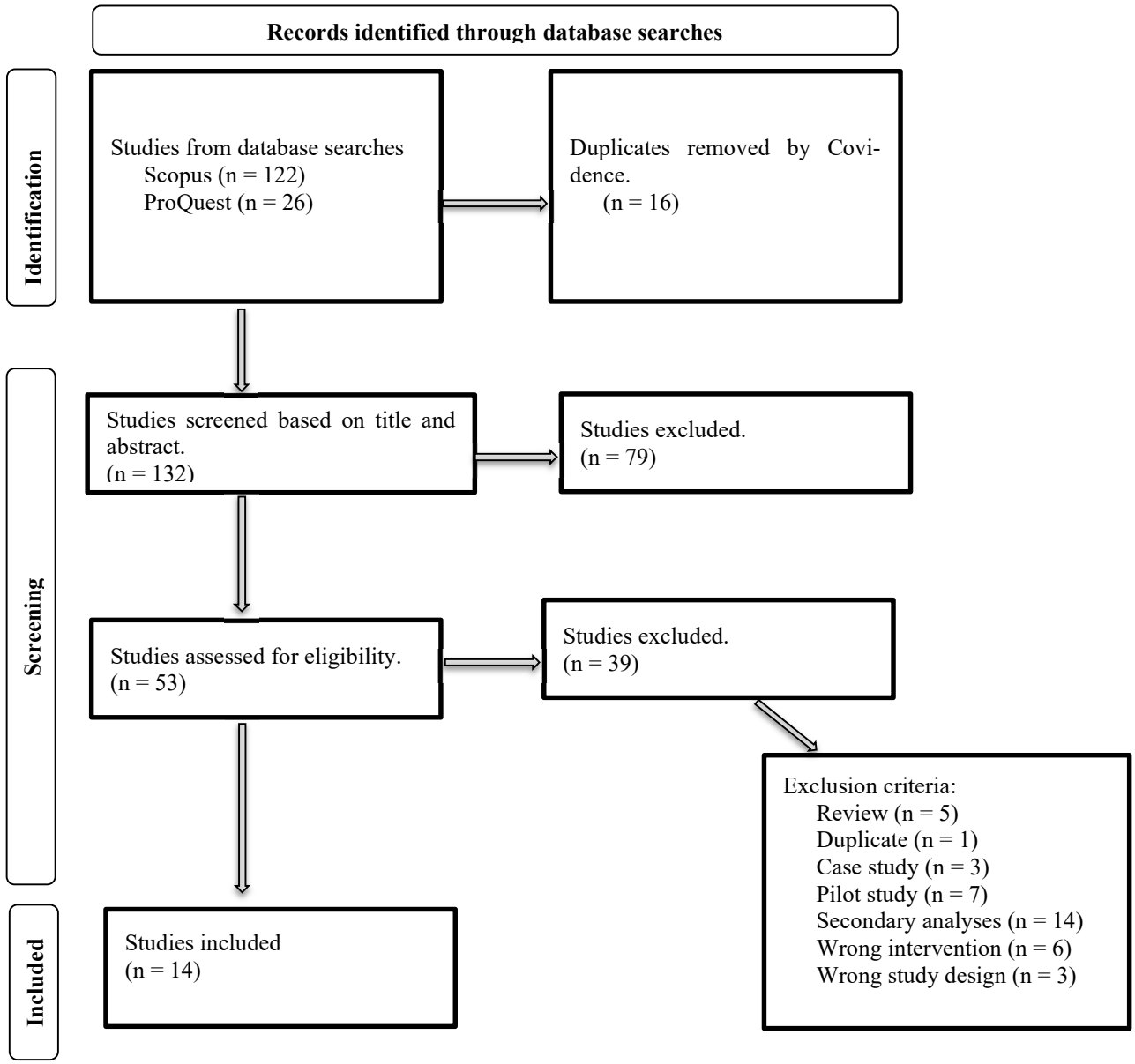
The databases for the study selection were Scopus and ProQuest. The search terms were: "virtual reality exposure therapy" OR "VRE*" AND "posttraumatic stress disorder" OR "PTSD". The search was limited so the search terms would have to be found in either title, abstract or keywords of the studies. The search was also limited to peer-reviewed articles, the written language to English and the published articles had to be from the last 20 years. In addition to the databases used, previously done relevant systematic and meta-analytic reviews on the efficacy of VRET were checked for additional studies that might have fallen outside the literature searches. In the final selection no such studies were found or included.

All the search items were imported and sorted using the citation programme Covidence. Duplicates were removed automatically by Covidence and manually during the selection process. At first the selected searches were reviewed for relevance on a title and abstract level. In the following stage studies were reviewed in full text to assess if they answered the research question.

The inclusion criteria for the study selection were the following. The study had to report relevant information on the effectiveness of VRET on a sample of clinically significant PTSD participants according to the DSM-IV or DSM-5 classification of PTSD. The assessment of PTSD symptoms had to be done using CAPS. Some of the exclusion criteria were the following (for a full list see Fig.1): secondary analysis of a sample in a previously done study, case-, pilot studies, predator journals or a “Julkaisufoorumi” (JUFO) classification of less than a 1 and studies using a differing intervention to VRET. As an exception two pilot studies were included in the final selection as they had medium to large sample sizes (n = 24-112) and their administration of VRET was similar to other studies included as well as their assessment of PTSD symptoms were done using the CAPS (Beidel et al., 2017; Difede et al., 2014). Notably the study by Reger et al., (2011) was excluded from the selection. Even though their VRET intervention was highly similar to those of the included studies, their assessment of PTSD symptoms

relied only on the PTSD-checklist (PCL) which is a self-report measure of a participant's PTSD symptoms. In addition, the studies utilizing VR but in the eye movement desensitization and reprocessing framework (EMDR & 3MDR) were also excluded as they fall away from the exposure therapy framework creating too much heterogeneity between methods and thus creating further difficulties in result interpretation.

Fig 1. PRISMA diagram



3 Results

3.1 Participant and study characteristics

In total, the selected studies had collectively 968 participants. In the selection 12 out of 14 selected studies enrolled current or former military personnel suffering from PTSD. In two of the selected studies the participants were present during the 2001 World trade center attacks (Difede et al., 2007, 2014). The sample sizes between studies ranged from 11 (Ready et al., 2010) to 192 (Difede et al., 2022) participants.

In almost all of the selected studies there was a skewed gender divide in the participants ranging from 76 % (Difede et al., 2014) to 100 % (Maples-Keller et al., 2019) being or identifying as male. As an exception in one of the studies, majority of the participants were or identified as female (n = 11, 73.3 %) (Loucks et al., 2019). The mean age of participants between selected studies ranged from 28 (McLay et al., 2011) to 46 years (Loucks et al., 2019).

The inclusion and exclusion criteria for participants enrolling in a VRET intervention were similar between studies. Most common exclusion criteria were serious medical illnesses, schizophrenia or other psychotic disorders, bipolar disorder, ongoing substance use disorders, suicide or self-harm risks and psychotropic medications had to be on a stable dosage (Beidel et al., 2017, 2019; Difede et al., 2007, 2022; Maples-Keller et al., 2019; McLay et al., 2011, 2017; Ready et al., 2010; Reger et al., 2016; Rothbaum et al., 2014).

There was still some variation in the exclusion criteria used, for instance in most studies if the participant was prescribed psychotropic medication the usage of such medication needed to be stable for at least two weeks. As an exception in one study that used benzodiazepines as a treatment tool, the other intervention groups had to discontinue their medication (Rothbaum et al., 2014).

In the literature reviewed two out of 14 studies used the newer CAPS-5 edition while the rest used the older fourth edition. When tested on a clinically significant sample there was a strong correlation between both editions' severity scores ($r = 0.83$). In addition, the interrater reliability between the two editions was strong ($k = 0.84$) (Weathers et al., 2018). Hence it can be expected

that when comparing studies that used either the fifth or fourth edition the comparability between these studies should be approached more cautiously but the strong convergent validity between the two editions should still allow for comparisons.

Out of the 14 studies selected three studies used a within-subjects design measuring the effectiveness of VRET (Beidel et al., 2017, 2019; Loucks et al., 2019). Four studies compared how different medication in conjunction with VRET affected VRET efficacy (Difede et al., 2014, 2022; Maples-Keller et al., 2019; Rothbaum et al., 2014). Rest of the selected studies either measured the efficacy of VRET against a passive and or active control group (Difede et al., 2007, 2022; McLay et al., 2017; Miyahira et al., 2012; Reger et al., 2016; Roy et al., 2014). In total eight out of 14 compared VRET to either a passive or active control group. In one of the studies an active control group condition utilized present-centered therapy while the others used some kind of trauma-focused therapy such as prolonged exposure therapy (PE). Of note the study comparing present-centered therapy to VRET was the only one to compare VRET to a non-trauma-focused intervention (Ready et al., 2010).

In addition, two of the selected studies also looked at physiological measures during the VRET exposure sessions, such as galvanic skin response, heart rate and salivary cortisol samples. These measurements were not part of the original study looking at VRET effectiveness but were instead followed-up with secondary analyses relating to the same sample (Katz et al., 2020; Norrholm et al., 2016).

3.2 VRET intervention and CAPS administration

VRET as an intervention was largely homogeneous in the selected studies. In all of the studies the intervention began with 1-2 introductory sessions without the use of VR exposure that were used largely to discuss the intervention and psychoeducation about PTSD. The introductory sessions then followed with exposure sessions. The number of sessions ranged from 6 (Rothbaum et al., 2014) to 14 (Beidel et al., 2019). The average number of sessions across all included studies was 9.4 sessions ranging from 90-120 minutes. The exposure session structure was similar between all the studies. Most commonly the session began with 30-45 minutes of exposure where the participant talked through their traumatic experiences while being immersed in the virtual reality environment that was controlled by the therapist to resemble the trauma, followed by 30 minutes of discussing the event. In some of the studies the VRET technology utilized

audiovisual stimulus while in others audiovisual stimulus was accompanied by tactile and olfactory stimuli if the traumatic memory included those senses (Maples-Keller et al., 2019; Reger et al., 2016).

The studies that differentiated from this structure were the ones using trauma management therapy (TMT) as a framework. The TMT framework similarly utilized the VRET elements but also added multiple sessions of group therapy following the exposure therapy (Beidel et al., 2017, 2019).

Four out of 14 selected studies reported using some kind of adherence check to see if the VRET was administered with the correct themes and practices (Beidel et al., 2017; Difede et al., 2014, 2022; Reger et al., 2016). CAPS administration was highly similar between studies. For instance, third party assessment of CAPS administrations during studies was common (Beidel et al., 2017; Difede et al., 2007; McLay et al., 2011; Reger et al., 2016; Rothbaum et al., 2014). The interrater reliability of CAPS administration showed kappa values of at least or more than $k > 0.8$.

3.3 Changes from pre- to posttreatment CAPS scores

As per the inclusion criteria all of the included studies reported pre- and posttreatment CAPS scores. The CAPS severity scores at pre-treatment ranged from 62.50 (Difede et al., 2007) to 95.2 (Beidel et al., 2017) assessed using the CAPS-IV (range of severity scores 0-136). In the studies using the CAPS-5 pre-treatment severity scores ranged from 35.58 (Maples-Keller et al., 2019) to 41.50 (Loucks et al., 2019) between the studies (range of severity scores 0-80). Two of the 14 included studies found no significant effect of VRET on posttreatment CAPS scores (Miyahira et al., 2012; Roy et al., 2014). In the rest of the studies all reported significant reductions in CAPS scores at posttreatment as a result of the VRET intervention. Average reductions in the CAPS-IV scores ranged from 13.3 (Miyahira et al., 2012) to 52.6 (Beidel et al., 2017) points and from 12.59 (Loucks et al., 2019) to 14.16 (Maples-Keller et al., 2019) in the studies using the CAPS-5 (for all the pre- and posttreatment CAPS scores see table 1).

3.4 Studies with a passive control group

Three of the selected studies used a passive control group as a comparison to VRET (Difede et al., 2007; Miyahira et al., 2012; Reger et al., 2016). A passive control group in all of the studies was a wait list condition with minimal attention. In one of the studies there was no significant difference between the control condition and VRET intervention (Miyahara et al., 2012). In the other two VRET showed a significant improvement in CAPS scores compared to the wait list condition (Difede et al., 2007; Reger et al., 2016).

3.5 Studies with an active control group

VRET was also compared to other forms of PTSD treatment. In total six studies compared VRET to other proven treatment forms with the most common comparison being traditional exposure therapy (Difede et al., 2022; McLay et al., 2017; Reger et al., 2016; Roy et al., 2014). In the selected studies four compared VRET to its traditional exposure therapy counterpart (Difede et al., 2022; McLay et al., 2017; Reger et al., 2016; Roy et al., 2014), one study compared VRET to present-centered therapy (Ready et al., 2010) and one to treatment as usual (a combination of different PTSD treatment forms) (McLay et al.,2011). In the studies comparing VRET to PE three found no significant differences between posttreatment CAPS scores and whether VRET or PE was used (Difede et al., 2022; McLay et al., 2017; Reger et al., 2016). One study found that VRET outperformed PE (Roy et al., 2014). However, the study in question had a smaller sample size compared to the aforementioned studies that found no significant difference between the efficacy of VRET and PE (see table 1. for sample sizes). In the other studies comparing VRET to other treatment methods, VRET outperformed “treatment as usual” group at posttreatment and in the other study VRET did not significantly reduce CAPS scores (McLay et al., 2011; Ready et al., 2010).

3.6 Studies with CAPS follow-up measurements

10 out of 14 studies included a follow-up condition in their study design (Beidel et al., 2017, 2019; Difede et al., 2007, 2014, 2022; Loucks et al., 2019; Maples-Keller et al., 2019; McLay et al., 2017; Reger et al., 2016; Rothbaum et al., 2014). The follow-up period ranged from 2-12 months. Eight out of the 10 studies that included a follow-up measurement found that VRET had significantly reduced CAPS scores at posttreatment and that these results were maintained at the follow-up assessment. In one of the studies that compared the efficacy of VRET to PE

found that in comparison to the VRET-group the PE-group saw significantly larger reduction in CAPS scores at both 3- and 6-month follow-ups (Reger et al., 2016).

3.7 Depression symptoms

In total nine studies also assessed VRET effect on depression symptoms. Two studies utilized the Hamilton depression rating scale and found that VRET reduces scores significantly at post-treatment as well as after 6 month-follow up (Beidel et al., 2017, 2019). Further seven studies utilized the Beck depression inventory (BDI) questionnaire. In three studies VRET had no significant effect on BDI scores (Difede et al., 2007; Miyahira et al., 2012; Ready et al., 2010). Meanwhile in the four others VRET intervention significantly reduced BDI scores at posttreatment but also when follow-up measurements were conducted (Difede et al., 2014, 2022; Maples-Keller et al., 2019; Reger et al., 2016).

An additional finding was that VRET was significantly more effective for participants with major depressive disorder and PE for non-depressed participants (Difede et al., 2022). In addition, in another study 71.4 % of participants with comorbid major depressive disorder had moved into recession as a result of VRET (Difede et al., 2014).

3.8 Drop-out rates and other outcome measures

As mentioned earlier exposure therapy forms have been criticized for their relatively high drop-out rates in comparison to other PTSD treatment forms (Lewis et al., 2020). In the selected studies the drop-out rates between exposure sessions were reported in Table 1. Depending on study drop-out rates ranged from 58.6% (Miyahira et al., 2012) to 4.7 % (Difede et al., 2007). Out of the 686 participants that were randomized to a VRET intervention group 203 dropped out of the intervention (29.6 %) in the selected studies of this review.

Additionally, two of the selected studies were analysed further using the physiological data collected during the study. In one analysis galvanic skin response (GSR) reduced in both PE and VRET groups of the (Reger et al., 2016) sample when compared to the physiological response of the wait list group when exposed to trauma related cues. However, there were no differences between VRET and PE group in GSR reduction (Katz et al., 2020). In the other secondary analysis salivary cortisol levels were recorded during and after the VRET interven-

tion of the (Rothbaum et al., 2014) sample. Their results reflected that VRET caused a significant reduction in salivary cortisol levels at posttreatment and 12-month follow-up when the participants were presented with a trauma-related cues (Norrholm et al., 2016; Rothbaum et al., 2014).

Table 1.

Study	Sample	Study design	Drop-out	Treatment duration	Outcome measures	Mean CAPS scores pre-& posttreatment
Beidel et al. 2017	n = 112	TMT + VRET	10.7 % n = 12	10 x 90-120 min VRET sessions	CAPS-IV: significant decrease in scores at posttreatment. Results were maintained after 3-, and 6-month follow-ups	95.2 & 42.6
Beidel et al. 2019	n = 92	TMT+VRET Vs VRET	33.7% n=31	14 x 90-120 min VRET treatment sessions	CAPS-IV: Significant decrease in both TMT+VRET and VRET groups. No significant differences between treatment groups.	83.5 & 33.5
Difede et al. 2007	n = 21	VRET vs WL	23.1% n = 3	6-13x 75 min sessions	CAPS-IV: VRET group showed significant reduction in scores compared to WL-group.	62.50 & 39.90
Difede et al. 2014	n = 25	VRET: DCS vs placebo	12% n = 3	12x 90min sessions	CAPS-IV: VRET + DCS showed greater symptom reduction than placebo after six-month follow-up	DCS: 81.62 & 32.38 Placebo: 75.08 & 42.17
Difede et al. 2022	n = 192	2x2-design DCS vs placebo, PE vs VRET	27.8% n=27	9 x 90min treatment sessions	CAPS-IV: Significant decrease in both PE and VRET groups after posttreatment and maintained after 3-month follow-up. No significant differences between treatment types.	73.13 & 52.42
Loucks et al. 2019	n = 15	VRET within-subjects design	26% n = 4	6-12x 90 min sessions	CAPS-V: Significant decrease in scores in pre- vs posttreatment measures. Results were maintained after 3-month follow-up	41.5 & 28.91
Maples-Keller et al. 2019	n = 27	VRET: Dexamethasone vs placebo	51.9% n = 14	6-11x 90 min sessions	CAPS-V: Significant decrease in scores in pre- vs posttreatment measures.	35.58 & 21.42
McLay et al. 2011	n = 20	VRGET vs TAU	5% n = 1	Up to 10 sessions of VRGET	CAPS-IV: VRGET showed significantly greater reduction in scores at posttreatment compared to TAU.	83.5 & 48.1
McLay et al. 2017	n = 74	VRET vs CET	16.3 % n = 7	8-12x 90 min sessions	CAPS-IV: Significant decrease in both CET and VRET groups after posttreatment and maintained at 3-month follow-up. No significant differences between treatment types.	76.8 & 65.7
Miyahira et al. 2012	n = 42	VRET vs MA	58.6% n = 17	8x VRET sessions	CAPS-IV: No significant differences in scores between the two groups	72.2 & 58.9
Ready et al. 2010	n =11	VRET vs PCT	9% n = 1	10x 90 min sessions	CAPS-IV: No significant reduction in scores in either group.	87.83 & 59.2
Reger et al. 2016	n = 162	VRET vs PE vs WL	44.4 % n = 24	10x 90-120 min sessions	CAPS-IV: Compared to WL both PE and VRET decreased scores significantly. No differences in PE vs VRET in posttreatment differences. PE showed significantly greater reduction in symptoms at 3- and 6-month follow-up compared to VRET	80.44 & 57.07
Rothbaum et al. 2014	n = 156	VRET: DCS vs alprazolam vs placebo	37.8% n = 59	6x 90 min sessions	CAPS-IV: VRET reduced scores significantly in all treatment conditions. This effect was maintained after 12-month follow-up	DCS: 85.3 & 65.9 Alprazolam: 88.0 & 69.6 Placebo: 82.6 & 63.8
Roy et al. 2014	n = 19	VRET vs PE	n.r.	12-20x 90 min sessions	CAPS-IV: VRET reduced CAPS scores significantly from pretreatment. PE group did not see a significant reduction in scores.	80.44 & 64.5

(CAPS = clinician administered PTSD scale, PCL = PTSD checklist, DCS = D-cycloserine, PE = prolonged exposure therapy, VRET = virtual exposure therapy, VRGET = virtual reality graded exposure therapy, TMT = trauma management therapy, CET = control exposure therapy, WL = waitlist, MA = minimal attention, TAU = treatment as usual, PCT = present-centered therapy , Drop-out rates were calculated using the total drop-out numbers compared to the amount of participants enrolled in a VRET group)

4 Discussion

4.1 Clinical implications of VRET

This systematic review supports the notion that VRET is an efficacious treatment for reducing PTSD symptoms. This review found that VRET reduces CAPS scores significantly and that in follow-up settings these results are maintained (Beidel et al., 2017, 2019; Difede et al., 2007, 2014, 2022; Loucks et al., 2019; Maples-Keller et al., 2019; McLay et al., 2017; Reger et al., 2016; Rothbaum et al., 2014). In addition, VRET reduced depression symptoms significantly in posttreatment settings and these results were retained when follow-up measures were done. This is a significant finding as MDD is highly comorbid with PTSD (Kessler et al., 1995).

From a theoretical perspective VRET should have a clear advantage in comparison to conventional exposure therapy in terms of emotional engagement. As mentioned, the immersive virtual reality environment offers the participant the opportunity to engage and recount their traumatic experiences which in the theoretical framework of emotional processing theory should boost therapeutic outcomes.

In support of this notion some secondary analyses have looked at how physiological response is mediated during VRET. In one analysis galvanic skin response (GSR) reduced in both PE and VRET groups of the (Reger et al., 2016) sample when compared to the physiological response of the wait list group when exposed to trauma related cues. However, there were no differences between VRET and PE group in GSR reduction (Katz et al., 2020). Additionally, in the other secondary analysis VRET caused a significant reduction in salivary cortisol levels at posttreatment and 12-month follow-up when presented with a trauma-related cues (Norrholm et al., 2016; Rothbaum et al., 2014).

These studies on physiological effects of VRET support the notion that VRET achieves some a significant level of habituation as reflected by reduced physiological response as well as significantly reduced CAPS scores (Reger et al., 2016; Rothbaum et al., 2014).

However, the promising results discussed in this review should be interpreted cautiously. A contradicting issue raised in the literature is that the VRET environment is immersive, but the VR-content may not match the traumatic event enough and thus the VR environment might even be seen as a distraction and a hinderance to emotional engagement (Reger et al., 2016). Furthermore, in the reviewed studies that compared VRET to PE: one found that VRET outperformed PE and two found no significant differences at posttreatment (Difede et al., 2022; McLay et al., 2017; Reger et al., 2016). In addition, in one of the studies conventional PE outperformed VRET at follow-up setting (Reger et al., 2016). These empirical contradictions raise the question of how justified is the use of VRET compared to its PE counterpart and the effectiveness of emotional processing theory in explaining the processes of PTSD treatment. From an additional perspective this issue is corroborated by the relative expenses of both methods. If VRET does not clearly show improved results compared to PE is the higher cost of VR-equipment and therapist training justified?

4.2 Limitations

A major limitation in the generalizability of these results is the lack of population validity in the selected study samples. A great majority of the participants were male former or current military service personnel. Hence comparability of VRET efficacy to a more representative PTSD-patient population is very difficult. Furthermore, this is a further reflection of the limitations of VRET as an intervention. Personalized VR-environments are expensive to construct and thus the participants are required to have a traumatic experience in a certain environment that can be replicated in VR for a large group of people. Traumatic experiences and memories are highly personal and currently the use of VRET requires similarity in traumatic experiences which limits the applicability of VRET.

As mentioned earlier a significant limitation of exposure therapies is their relatively high drop-out rate. In this review the selected studies resulted in a pooled drop-out rate of 29.6 % in those participants enrolled in a VRET intervention group. In comparison to a large-scale meta-analysis of PTSD treatment forms. In their review of 116 PTSD clinical studies, Lewis et al. (2020) found a pooled drop-out rate of 16 % which is markedly lower than the pooled drop-out rate of 29.6 % found in this review. They found a further significant association between trauma-focused interventions and higher drop-out rates (Lewis et al., 2020).

Although this trend of higher drop-out rates in trauma-focused interventions like VRET and PE is concerning, some of the studies have argued that this relatively high drop out rate might be a reflection of the poor population validity in the studies. 12 out of 14 selected studies in this review used a male majority sample of military personnel and veterans. Many of these selected studies referred to a cohort study of American soldiers with PTSD that found that the utilization of mental health services is very low and that the drop-out of this specific trauma-population is relatively high when compared to non-military PTSD population (Hoge et al., 2014).

4.3 Future directions

In most of the studies VRET followed rigorous PE guidelines for administration. As mentioned before the exposure in PE and VRET differs quite drastically from each other. It calls into question whether the PE- structure is as valid for VRET as it is for conventional exposure therapy. Could VRET as an intervention benefit from its own therapeutic guidelines in relation to the VR-exposure?

Future research should also include comparison of VRET to other proven efficacious PTSD treatment forms and how VRET interacts as a treatment form in a more representative PTSD population. In the studies reviewed VRET was only compared to conventional exposure therapy and two other treatment forms (present-centered therapy and treatment as usual group). With the latter two studies having small sample sizes (McLay et al., 2011; Ready et al., 2010). VRET should be compared to other proven PTSD treatment forms using rigorous RCT settings and larger sample sizes. Furthermore, only one of the selected studies compared VRET to a non-trauma-focused treatment form of PTSD. Additional research should compare how VRET performs when compared to non-trauma-focused treatment, as for instance as mentioned a review assessing drop-out rates have shown that trauma-focused treatment forms have higher drop-out rates when compared to non-trauma-focused (Lewis et al., 2020).

In conclusion, VRET in the light of this review and its research question looks to be an efficacious form of PTSD treatment in terms of outcome measures such as PTSD symptoms but also secondary measures such as comorbid depression symptoms. However, this claim is hindered by major limitations in population validity and increased drop-out rates when compared to other efficacious treatment forms of PTSD. These limitations have a limiting effect on the generalizability of VRET as an PTSD intervention.

References

Atwoli, L., Stein, D. J., Koenen, K. C., & McLaughlin, K. A. (2015). Epidemiology of post-traumatic stress disorder: prevalence, correlates and consequences. *Current Opinion in Psychiatry*, *28*(4), 307–311. https://doi.org/10.1097/YCO.0000000000000167

Beidel, D. C., Frueh, B. C., Neer, S. M., Bowers, C. A., Trachik, B., Uhde, T. W., & Grubaugh, A. (2019). Trauma management therapy with virtual-reality augmented exposure therapy for combat-related PTSD: A randomized controlled trial. *Journal of Anxiety Disorders*, *61*, 64–74. https://pc124152.oulu.fi:9443/login?url=https://search.ebscohost.com/login.aspx?direct=true&db=asn&AN=134088505&site=ehost-live&scope=site

Beidel, D. C., Frueh, B. C., Neer, S. M., & Lejuez, C. W. (2017). The efficacy of trauma management therapy: A controlled pilot investigation of a three-week intensive outpatient program for combat-related PTSD. *Journal of Anxiety Disorders*, *50*, 23–32. https://doi.org/10.1016/j.janxdis.2017.05.001

Black, D. W., Grant, J. E., & Association, A. P. (2014). *DSM-5 guidebook : the essential companion to the diagnostic and statistical manual of mental disorders* (Fifth edition). American Psychiatric Publishing.

Carl, E., Stein, A. T., Levihn-Coon, A., Pogue, J. R., Rothbaum, B., Emmelkamp, P., Asmundson, G. J. G., Carlbring, P., & Powers, M. B. (2019). Virtual reality exposure therapy for anxiety and related disorders: A meta-analysis of randomized controlled trials. *Journal of Anxiety Disorders*, *61*, 27–36. https://doi.org/10.1016/j.janxdis.2018.08.003

Carlson, E. B., Dalenberg, C., & McDade-Montez, E. (2012). Dissociation in posttraumatic stress disorder part I: Definitions and review of research. *Psychological Trauma*, *4*(5), 479–489. https://doi.org/10.1037/a0027748

Deng, W., Hu, D., Xu, S., Liu, X., Zhao, J., Chen, Q., Liu, J., Zhang, Z., Jiang, W., Ma, L., Hong, X., Cheng, S., Liu, B., & Li, X. (2019). The efficacy of virtual reality exposure therapy for PTSD symptoms: A systematic review and meta-analysis. *Journal of Affective Disorders*, *257*, 698–709. https://doi.org/https://doi.org/10.1016/j.jad.2019.07.086

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. *The Journal of Clinical Psychiatry*, *68*(11), 1639. https://doi.org/10.4088/JCP.v68n1102

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*, *39*(5), 1052–1058. https://doi.org/10.1038/npp.2013.317

Difede, J., Rothbaum, B. O., Rizzo, A. A., Wyka, K., Spielman, L., Reist, C., Roy, M. J., Jovanovic, T., Norrholm, S. D., Cukor, J., Olden, M., Glatt, C. E., & Lee, F. S. (2022). Enhancing exposure therapy for posttraumatic stress disorder (PTSD): a randomized clinical trial of virtual reality and imaginal exposure with a cognitive enhancer. *Translational Psychiatry*, *12*(1), 299. https://doi.org/10.1038/s41398-022-02066-x

Foa, E. B., & Hearst-Ikeda, D. (1996). Emotional dissociation in response to trauma. In L. K. Michelson & W. J. Ray (Eds.), *Handbook of Dissociation: Theoretical, Empirical, and Clinical Perspectives* (pp. 207–224). Springer US. https://doi.org/10.1007/978-1-4899-0310-5_10

Foa, E. B., & Kozak, M. J. (1986). Emotional processing of fear: exposure to corrective information. *Psychological Bulletin*, *99*(1), 20–35. https://doi.org/10.1037/0033-2909.99.1.20

Friedman, M. J., Resick, P. A., Bryant, R. A., & Brewin, C. R. (2011). Considering PTSD for DSM-5. *Depression and Anxiety*, *28*(9), 750–769. https://doi.org/10.1002/da.20767

Hoge, C. W., Grossman, S. H., Auchterlonie, J. L., Riviere, L. A., Milliken, C. S., & Wilk, J. E. (2014). PTSD treatment for soldiers after combat deployment: low utilization of mental health care and reasons for dropout. *Psychiatric Services (Washington, D.C.)*, *65*(8), 997–1004. https://doi.org/10.1176/appi.ps.201300307

Katz, A. C., Norr, A. M., Buck, B., Fantelli, E., Edwards-Stewart, A., Koenen-Woods, P., Zetocha, K., Smolenski, D. J., Holloway, K., Rothbaum, B. O., Difede, J., Rizzo, A., Skopp, N., Mishkind, M., Gahm, G., Reger, G. M., & Andrasik, F. (2020). Changes in physiological reactivity in response to the trauma memory during prolonged exposure and virtual reality exposure therapy for posttraumatic stress disorder. *Psychological Trauma*, *12*(7), 756–764. https://doi.org/10.1037/tra0000567

Keane, T. M., Marshall, A. D., & Taft, C. T. (2006). Posttraumatic stress disorder: etiology, epidemiology, and treatment outcome. *Annual Review of Clinical Psychology*, *2*, 161. https://doi.org/10.1146/annurev.clinpsy.2.022305.095305

Kessler, R. C., Sonnega, A., Bromet, E., Hughes, M., & Nelson, C. B. (1995). Posttraumatic stress disorder in the national comorbidity survey. *Archives of General Psychiatry*, *52*(12), 1048. https://doi.org/10.1001/archpsyc.1995.03950240066012

Kothgassner, O. D., Goreis, A., Kafka, J. X., Van Eickels, R. L., Plener, P. L., & Felnhofer, A. (2019). Virtual reality exposure therapy for posttraumatic stress disorder (PTSD): a meta-analysis. *European Journal of Psychotraumatology*, *10*(1), 1654782. https://doi.org/10.1080/20008198.2019.1654782

Lang, P. J. (1977). Imagery in therapy: an information processing analysis of fear. *Behavior Therapy*, *8*(5), 862–886. https://doi.org/https://doi.org/10.1016/S0005-7894(77)80157-3

Lanius, R. A., Brand, B., Vermetten, E., Frewen, P. A., & Spiegel, D. (2012). The dissociative subtype of posttraumatic stress disorder: rationale, clinical and neurobiological evidence, and implications. *Depression and Anxiety*, *29*(8), 701–708. https://doi.org/https://doi.org/10.1002/da.21889

Lewis, C., Roberts, N. P., Gibson, S., & Bisson, J. I. (2020). Dropout from psychological therapies for post-traumatic stress disorder (PTSD) in adults: systematic review and meta-analysis. *European Journal of Psychotraumatology*, *11*(1), 1709709. https://doi.org/10.1080/20008198.2019.1709709

Loucks, L., Yasinski, C., Norrholm, S. D., Maples-Keller, J., Post, L., Zwiebach, L., Fiorillo, D., Goodlin, M., Jovanovic, T., Rizzo, A. A., & Rothbaum, B. O. (2019). You can do that?!: Feasibility of virtual reality exposure therapy in the treatment of PTSD due to military sexual trauma. *Journal of Anxiety Disorders*, *61*, 55–63. https://doi.org/10.1016/j.janxdis.2018.06.004

Maples-Keller, J. L., Jovanovic, T., Dunlop, B. W., Rauch, S., Yasinski, C., Michopoulos, V., Coghlan, C., Norrholm, S., Rizzo, A. S., Ressler, K., & Rothbaum, B. O. (2019). When translational neuroscience fails in the clinic: Dexamethasone prior to virtual reality exposure therapy increases drop-out rates. *Journal of Anxiety Disorders*, *61*, 89–97. https://doi.org/10.1016/j.janxdis.2018.10.006

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. *Cyberpsychology, Behavior and Social Networking*, *20*(4), 218–224. https://doi.org/10.1089/cyber.2016.0554

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. *Cyberpsychology, Behavior and Social Networking*, *14*(4), 223–229. https://doi.org/10.1089/cyber.2011.0003

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. *Studies in Health Technology and Informatics*, *181*, 128. https://doi.org/10.3233/978-1-61499-121-2-128

Norrholm, S. D., Jovanovic, T., Gerardi, M., Breazeale, K. G., Price, M., Davis, M., Duncan, E., Ressler, K. J., Bradley, B., Rizzo, A., Tuerk, P. W., & Rothbaum, B. O. (2016). Baseline psychophysiological and cortisol reactivity as a predictor of PTSD treatment outcome in virtual reality exposure therapy. *Behaviour Research and Therapy*, *82*, 28–37. https://doi.org/10.1016/j.brat.2016.05.002

Rachman, S. (1980). Emotional processing. *Behaviour Research and Therapy*, *18*(1), 51. https://doi.org/10.1016/0005-7967(80)90069-8

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. *Cyberpsychology, Behavior and Social Networking*, *13*(1), 49. https://doi.org/10.1089/cyber.2009.0239

Reger, G. M., Holloway, K. M., Candy, C., Rothbaum, B. O., Difede, J., Rizzo, A. A., & Gahm, G. A. (2011). Effectiveness of virtual reality exposure therapy for active duty soldiers in a military mental health clinic. *Journal of Traumatic Stress*, *24*(1), 93–96. https://doi.org/10.1002/jts.20574

Reger, G. M., Koenen-Woods, P., Zetocha, K., Smolenski, D. J., Holloway, K. M., Rothbaum, B. O., Difede, J., 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). *Journal of Consulting and Clinical Psychology*, *84*(11), 946–959. https://doi.org/10.1037/ccp0000134

Rothbaum, B. O., & Hodges, L. F. (1999). The use of virtual reality exposure in the treatment of anxiety disorders. *Behavior Modification*, *23*(4), 507–525. https://doi.org/10.1177/0145445599234001

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. *The American Journal of Psychiatry*, *171*(6), 640–648. https://doi.org/10.1176/appi.ajp.2014.13121625

Roy, M. J., Costanzo, M. E., Blair, J. R., & Rizzo, A. A. (2014). *Compelling evidence that exposure therapy for PTSD normalizes brain function*. https://doi.org/10.3233/978-1-61499-401-5-61

Shalev, A. Y., Freedman, S., Peri, T., Brandes, D., & Sahar, T. (1997). Predicting PTSD in trauma survivors: Prospective evaluation of self-report and clinician-administered instruments. *The British Journal of Psychiatry*, *170*, 558–564. https://www.proquest.com/scholarly-journals/predicting-ptsd-trauma-survivors-prospective/docview/274852075/se-2?accountid=13031

Weathers, F. W., Bovin, M. J., Lee, D. J., Sloan, D. M., Schnurr, P. P., Kaloupek, D. G., Keane, T. M., & Marx, B. P. (2018). The clinician-administered PTSD scale for DSM-5 (CAPS-5): Development and initial psychometric evaluation in military veterans. *Psychological Assessment*, *30*(3), 383–395. https://doi.org/10.1037/pas0000486

Weathers, F. W., Keane, T. M., & Davidson, J. R. T. (2001). Clinician-administered PTSD scale: A review of the first ten years of research. *Depression and Anxiety*, *13*(3), 132–156. https://doi.org/10.1002/da.1029

Weathers, F. W., Marx, B. P., Friedman, M. J., & Schnurr, P. P. (2014). Posttraumatic Stress Disorder in DSM-5: New criteria, new measures, and implications for assessment. *Psychological Injury and Law*, *7*(2), 93–107. https://doi.org/10.1007/s12207-014-9191-1