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ANXIETY DISORDERS (A PELISSOLO, SECTION EDITOR)

Recent Progress in Virtual Reality Exposure Therapy for Phobias: A Systematic Review

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Abstract This review is designed to systematically examine the available evidence about virtual reality exposure therapy's (VRET) efficacy for phobias, critically describe some of the most important challenges in the field and discuss possible directions. Evidence reveals that virtual reality (VR) is an effective treatment for phobias and useful for studying specific issues, such as pharmacological compounds and behavioral manipulations, that can enhance treatment outcomes. In addition, some variables, such as sense of presence in virtual environments, have a significant influence on outcomes, but further research is needed to better understand their role in therapeutic outcomes. We conclude that VR is a useful tool to improve exposure therapy and it can be a good option to analyze the processes and mechanisms involved in exposure therapy and the ways this strategy can be enhanced. In the coming years, there will be a significant expansion of VR in routine practice in clinical contexts.

Keywords Virtual reality · Mixed realities · Psychological treatments · Phobias interventions · Systematic review

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Introduction

Virtual reality (VR) is a technology that makes it possible to generate "analogues" of the real world. It consists of computer-generated worlds that can be practically indistinguishable from the real world. Through this technology, it is possible to create artificial experiences in real time, making the user feel immersed and able to interact as if it were the real world. VR can generate new forms of human-machine interaction, as the media become part of ourselves, *extensions of the senses* [1]. VR users come to believe that the experience is real and that they are really there. VR's capacity to make users feel like they are in a certain place and having meaningful experiences raises numerous possibilities for psychology [2, 3].

Currently, VR is considered an effective tool for the treatment of many psychological problems [4]. These potential uses are related to two advantages of VR: the control it allows and its great flexibility. Creating virtual worlds provides great possibilities that can even surpass reality. Moreover, the user will always be safe and protected in these synthetic worlds.

Since the first publications in the early 1990s, numerous clinical trials have been carried out, and reviews and meta-analytic studies have provided evidence about VR's usefulness for various clinical conditions (e.g., anxiety disorders, stress-related disorders, psychosis, eating disorders, and health conditions). In particular, VR's efficacy has been most striking in the area of phobias, especially in carrying out exposure therapy. Exposure therapy is considered the "gold standard" evidence-based technique for these disorders, but it may be difficult to accept and is sometimes rejected by patients because they consider it too aversive. VR exposure therapy (VRET) can overcome or mitigate this problem by producing greater user acceptance and providing control and access to situations where exposure therapy would be uncontrollable

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(fear of flying); difficult to access (open spaces, being far from home, going to another country in an agoraphobic patient); or simply inaccessible (fear of ghosts, specific past or future situations). VRET is not considered a new form of therapy, but rather a technological adjunct [5] that can help the clinician to apply treatments more ecologically and effectively [6].

This paper aims to address the following objectives: examine the available evidence about VRET efficacy for phobias published in the past 5 years through a systematic review, critically describe some of the most important achievements and challenges in the field, and discuss possible future perspectives for VRET developments in Clinical Psychology. Findings regarding augmented reality (AR), a tool that blends both virtual and real-world elements, are also considered for this study.

Method

Study Selection

The PRISMA guidelines for systematic reviews and meta-analyses were employed to conduct a literature search [7]. All studies on VRET for phobias in the past 5 years were included in the first scope of the search criteria. Randomized control trials (RCT) were included following these criteria: (1) participants had a diagnosis of a phobia, (2) VRET was applied to intervene on the clinical symptoms, (3) there were at least ten participants in each experimental condition, (4) articles were published in English or Spanish, and (5) articles were published in peer-reviewed journals.

Data Sources and Searches

Major medical, health, and psychological literature databases, including PsycNet, PubMed, Scopus, and Web of Science, were utilized. Search criteria included all publications from 2012 to January 2017. Although the entry style for keywords was modified depending on the requirements of each database, the following keywords were used: "virtual reality exposure therapy" OR "virtual reality" OR "augmented reality" combined with phob* OR arachnophobia OR "social anxiety disorder" OR agoraphobia OR "fear flying" OR acrophobia OR "fear of falling."

Systematic and narrative reviews, meta-analyses, protocols, case studies, studies on change processes and mechanisms, and any other sources of evidence (theoretical or empirical) were retrieved and classified into categories to update the cutting-edge research in the field. However, all these articles were excluded from the principal analysis based on the systematic review of RCT on the efficacy or effectiveness of VRET for phobias.

Upon completion of the search, titles and abstracts of the identified articles were assessed for suitability for the review. Then, full texts of the suitable articles were retrieved for further examination of their contents. The reference lists of the selected articles, as well as previous systematic reviews and meta-analyses, were also examined for additional publications that might have been overlooked in the search. Titles and abstracts of all the papers identified through the search were read. The full texts of studies that appeared to meet the inclusion criteria were then independently reviewed and screened by two researchers to establish their relevance, in addition to studies with insufficient information in the title and abstract. Any discrepancies between the researchers were resolved through discussion and final agreement.

Results

Virtual Reality Exposure Efficacy

Meta-analysis and Reviews

In the last 5 years, one meta-analysis on VRET efficacy was conducted [8]. This study doubled the total number of participants from previous studies [9, 10] and incorporated new methodological tools for data analysis, although with a limitation regarding the small sample size. Recently, another meta-analysis has been conducted [11••], but focusing on the generalizability of the results to real-life situations. This study used an innovative approach, incorporating only those studies that included behavioral tests and, thus, trying to avoid self-report biases. Finally, Ling, Nefs, Morina, Heynderickx, and Brinkman [12••] presented the first meta-analysis on the relationship between sense of presence and anxiety during VRET, confirming a positive relationship between them. The study's main strength lies in presenting moderators that may be useful for clinical application.

With regard to systematic reviews, two studies [13, 14] presented data coinciding with previous evidence, showing the overall efficacy of VRET and providing a broader scope because not only phobias were included. However, Turner and Casey [13] included few studies and failed to incorporate an important moderator, such as the sense of presence in VR. A major limitation of Valmaggia et al. [14] stems from the rather limited qualitative synthesis of the studies included. All these studies showed a clear superiority of VRET versus non-active control groups, and equal or even slightly greater efficacy than other active control groups (mainly in vivo exposure within a CBT protocol). Despite all these efforts, not all meta-analyses and reviews achieve high-quality standards [6]. It must be pointed out that a further systematic review focused on AR was conducted within the last 5 years [15]. It constitutes the first review that examines the use of AR in psychological

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disorders. All the studies conducted with AR are on phobias and although AR seems to be a promising tool, the field is still in its infancy to establish conclusive statements.

Randomized Controlled Trials in the Past 5 Years

The search resulted in 124 citations, of which 97 were not considered relevant for this review. A description of the process followed and reasons for excluding studies are presented in the flowchart (Fig. 1). A total of 27 articles were selected after examination of the abstracts. Following an in-depth analysis of the full text, 11 of them met the inclusion criteria. The studies were conducted in different countries: one in the USA [16], one in Canada [20], three in Spain [18•, 35, 36], one in France [32], two in the Netherlands [22•, 29], one in Rumania [31], one in Italy [37], and one in Australia [25].

As Table 1 shows, a total of 11 RCTs [16, 18•, 20, 22•, 25, 29, 31, 32, 35–37] analyzing the efficacy of VRET were carried out. Ten studies focused on VR and only one used a variant of VR (augmented reality). As for the disorders addressed, three studies focused on social anxiety disorder [16, 20, 22•]; five on agoraphobia (including or not panic disorder) [25, 29, 32, 35, 36]; one on small animal phobia [18•]; one on different phobias (social anxiety disorder, flying phobia, and

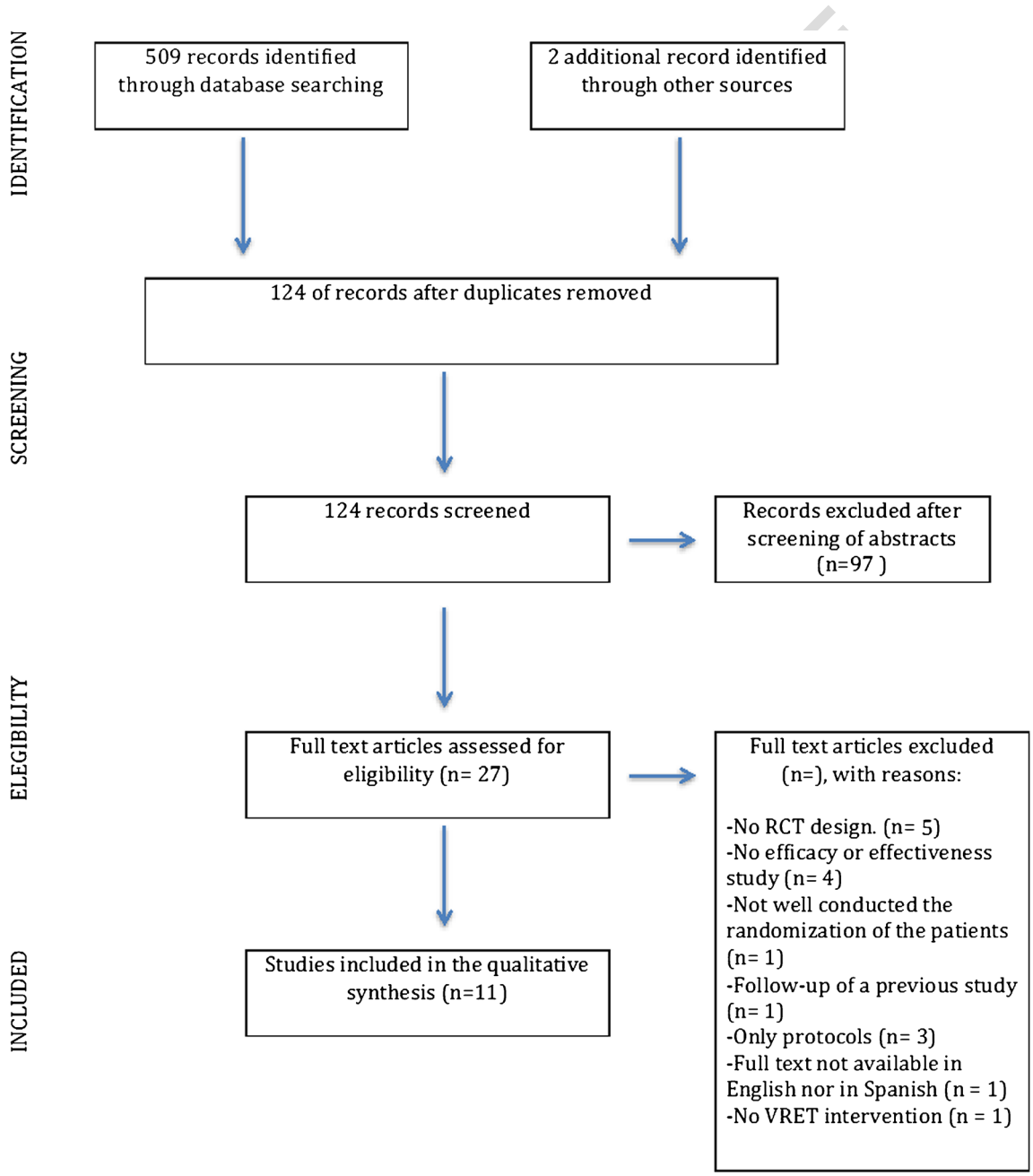

Fig. 1 Identifying relevant works: flow chart of systematic review and reasons for inclusion and exclusion

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acrophobia) [31]; and one on fear of flying [37]. In all of them, the experimental conditions for comparison were evidence-based treatments and were compared to active conditions or a waiting list (WL). The sample size was small in all studies, and no sub-sample exceeded 35 participants. Regarding other methodological issues, Table 1 presents the specific items on the CONSORT checklist for each RCT.

Overall, VRET conditions showed to be significantly more efficacious than non-active control conditions (WL). This is the case for all disorders and all studies, except from panic disorder in which only one study was conducted [32] showing no significant differences between conditions. It is interesting to point out that this study is one of the few ones that is constituted by a large sample which is one of the major flaws in the field and thus it may be an explanatory factor of the absence of differences.

With respect to the overall comparison of VRET conditions to active conditions, there is a pattern that shows no significant differences between the conditions taking into consideration diverse active conditions and a number of mental disorders, with just few exceptions. This is consistent with the principal aim of VR treatments. That is, not to greatly surpass the effect sizes of traditional approaches but to equal the effects taking into account the vast array of advantages that VRET entail and explained elsewhere, for example [6]. Bouchard et al. [20] is the only study presenting findings in favor of VRET condition. On the contrary, just Kampmann et al. [22•], Botella et al. [18•], and Meyerbröker et al. [29] present results in favor of the in vivo condition. Nevertheless, there are vital differences between the studies to be stressed. While Kampmann's study [22•] tends to lessen the results (the follow-up shows a significant difference in favor of in vivo), Botella's study [18•] shows to be equally efficacious in the follow-up measurements and Meyerbröker's study [29] only presents results favoring in vivo condition above VRET condition in one out of four measures. Besides, Botella's study [18•] has been conducted utilizing AR which may behave in a different way compared to VR. In any case, all these conclusions must be taken with caution and thus quantitative meta-analytical studies should test these descriptive assumptions.

Relevant Issues and Challenges of VR

Sense of Presence and Treatment Outcomes

The sense of presence in VR environments has been intensively researched, but there has been considerable discussion about its definition (e.g., [38–44]). As Diemer et al. [45] pointed out, theories of presence can be divided into descriptive and structural models. Descriptive models focus on delimitating the components of presence (e.g., [46, 47]). From this perspective, presence has been considered a multidimensional construct that includes different aspects, such as spatial presence, social presence, co-presence, involvement, realness, and so on. By contrast, structural models focus on explaining how presence is generated in users (e.g., [48, 49]).

In spite of this controversy, many authors have suggested that this illusion is a key ingredient in achieving success in VRET [9, 50–53]. However, research on the influence of presence on treatment outcome has produced mixed results. Krijn et al. [54] manipulated presence using a head-mounted display (HMD) (low presence) or a computerized automatic virtual environment (CAVE) (high presence), finding no differences between the two conditions in the efficacy of VRET for acrophobia. However, this study did not assess presence directly, but instead only manipulated it [55]. In fact, the authors found that participants who dropped out early experienced less presence and did not feel anxiety in the virtual environment, compared to completer patients. Price and Anderson [56] reported similar results for fear of flying: presence contributed to the experience of anxiety, and it was associated with peak fear ratings during the first VRET session, but they did not find a relationship between presence and treatment response. They concluded that sense of presence may be a necessary but insufficient variable for successful VRET. However, this study assessed presence using a unidimensional measure [55]. Hence, they [55] examined the associations between presence (and its constituents: spatial presence, involvement, realness); fear ratings; and treatment response in a social phobia sample. Findings showed that global presence and the realness factor were related to fear scores. Nevertheless, spatial presence did not show associations with fear scores or treatment response. Finally, only the involvement factor significantly predicted treatment response. As involvement is related to attention to the environment, the authors suggested that these results agreed with proposed mechanisms of exposure therapy, demonstrating that sustained attention during exposure is associated with better treatment responses [55].

Because experiencing anxiety is considered a key requisite for effective exposure therapy, many authors have suggested that presence-treatment outcome relationships could be influenced by presence-anxiety correlations. However, studies show unclear relationships between presence and emotions. Some studies found significant positive correlations, [56, 57], some did not [54, 58, 59], and some even found negative correlations [60, 61]. Ling et al.'s meta-analysis [12] examined the relationship between presence and anxiety during VRET, identifying 33 papers with a total of 1.196 participants. They also examined potential moderators (characteristics of the technology, sample, disorder, and study design). This meta-analysis confirmed the positive relationship between presence and anxiety, and that this relationship is influenced by several moderating factors (with a large relationship for fear of animals and fear of flying, moderate for acrophobia, and small for social anxiety disorder). In addition, presence-anxiety correlations were stronger for clinical populations

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Q2 **Table 1** RCTs analyzing the efficacy of VRET and the specific items on the CONSORT checklist for each RCT

Study	Number (F/M)	Age	Clinical sample	Condition (*N*)	Sessions	Primary outcome measure	Post-assessment	Description of protocol utilized
Anderson et al. [16]	97 (60/37)	19–60 M = 39	SAD	−1: VRE (*n* = 25) −2: EGT (*n* = 25) −3: WL (*n* = 25)	8	PRCS FNE-B	Post: (1 = 2) > 3 12 m: (1 = 2) > 3	VRE = Anderson et al. [16]; Hofmann [17]
Botella et al. [18•]	63 (59/4)	20–70 M = 31, 73	Small animals phobia	−1: IVE (*n* = 31) −2: ARS (*n* = 32)	1	BAT	Post: 1 > 2 3 m: 1 = 2 6 m: 1 = 2	"One-session treatment" (Öst) [19]
Bouchard et al. [20]	59 (43/16)	M = 34, 5	SAD	−1: CBT + VR: (*n* = 17) −2: CBT (*n* = 22) −3: WL (*n* = 20)	14	LSAS-SR	Post: 1 > 2 > 3 6 m: 1 > 2 > 3	Clark and Wells [21]
Kampmann et al. [22•]	60 (38/22)	M = 36, 88	SAD	−1: VRET (*n* = 20) −2: iVET (*n* = 20) −3: WL (*n* = 20)	10	LSAS-SR FNE-B	Post: (1 = 2) > 3 3 m: 2 > 1 > 3	Scholing and Emmelkamp [23] and Hofmann and Otto [24]
Malbos et al. [25]	19 (12/7)	M = 44.11	Panic disorder with agoraphobia	1: VRET 2: VRET + CBT	10	DASS ASI ACQ MIA	Post: 1 = 2 Follow up: 1 = 2	Barlow [26]; Beck and Emery [27]; Craske [28]
Meyerbroeker et al. [29]	55	18–65	Agoraphobia	1: VRET (*n* = 19) 2: iVET (*n* = 18) 3: WL (*n* = 18)	10	ACQ PDSS BSQ MIA	PDSS: 2 > 1 > 3 ACQ, BSQ, MIA: Post: (1 = 2) > 3	Craske and Barlow [30]
Moldovan and David [31]	32 (15/17)	Over 18	Flying phobia (*n* = 9); Social anxiety disorder (*n* = 15); Acrophobia (*n* = 8)	1: VRCBT (*n* = 16) 2: WL (*n* = 16)	1	LSAS FAS FAM STAI FNE-B SSPS	Post: 1 = 2 Follow up (unspecified when): 1 = 2	"One-session treatment" (Öst) [19] CBT: REBT theory
Pelissolo et al. [32]	92 (62/30)	24–72 M = 37, 1	Panic disorder with agoraphobia	1: VRET (*n* = 29) 2: CBT (*n* = 31) 3: WL (*n* = 32)	12	FQ PDSS CAS PPGAS STAI HARS BDI WSA SDS	Post: no dif 3 m: no dif 6 m: no dif 12 m: no dif	Cottraux et al. [33] and Landon and Barlow [34]
Peñate Castro et al. [35]	80	24–60	Chronic agoraphobia	1: VRET (*n* = 30) 2: CBTgroup (*n* = 30) 3: Medication (*n* = 20)	11	ACQ BSQ BAI LSAS SUA BAT	Post: VRET > (CBT group = medication 6 m Post: VRET > (CBTgroup = medication)	Unspecified
Pitti et al. [36]	99	M = 39	Agoraphobia	1: PX-CBT (*n* = 27) 2: PX-CBT-VRET (*n* = 27)	11	AGPH ACQ BSQ	Post:(1 = 2) > 3 6 m: 1 = 2	Unspecified

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Table 1 (continued)

Study	Number (F/M)	Age	Clinical sample	Condition (*N*)	Sessions	Primary outcome measure	Post-assessment	Description of protocol utilized
				3: PX (*n* = 32)		BAI BDI-II		
Triscari et al. [37]	65	24–70 M = 43, 52	Fear of flying	1: CBT-SD (systematic desensitization) (*n* = 22) 2: CBT – EMRD (*n* = 22) 3: CBT – VRET (*n* = 21)	10	FAS FAM	Post: 1 = 2 = 3 12 m: 1 = 2 = 3	Unspecified

F feminine, *M* masculine, *VRE* virtual reality exposure, *EGT* exposure group therapy, *WL* waiting list, *PRCS* self-report of public speaking fears, *FNE-B* self-report of social anxiety disorder symptoms, *IVE* in vivo exposure, *AGS* augmented reality system, *BAT* behavioral avoidance test, *SAD* social anxiety disorder, *CBT + VR* cognitive behavioral therapy plus virtual reality, *LSAS-SR* Liebowitz social anxiety scale-self report, *VRET* virtual reality exposure therapy, *iVET* in vivo exposure therapy, *DASS* depression anxiety stress scale, *ASI* anxiety sensitivity index, *MIA* mobility inventory for agoraphobia, *ACQ* agoraphobic cognitions questionnaire, *BSQ* body sensations questionnaire, *PDSS* panic disorder severity scale, *FAS* flight anxiety situations, *FAM* flight anxiety modality, *STAI* state and trait anxiety questionnaire, *SPSS* self statements during public speaking scale; *FQ* fear questionnaire, *REBT theory* rational emotive behavior therapy, *CAS* Chambless agoraphobic cognitions, *PPGAS* panic, phobia and generalized anxiety scale, *HARS* Hamilton anxiety rating scale, *BDI* Beck depression inventory, *WSA* work and social adjustment scale, *SDS* Sheehan disability scale, *BAI* Beck anxiety inventory, *SUA* subjective units of anxiety, *PX* paroxetine, *SD* systematic desensitization, *EMRD* eye movement desensitization and reprocessing

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than for non-clinical populations. Finally, moderating effects were found for some technology characteristics.

Although significant correlations between presence and anxiety have been reported, it remains unclear why they are related [62]. It is not clear whether users' pre-existing anxiety increases their likelihood of feeling present or if an anxiety-inducing virtual environment enhances presence. A causal influence of fear or anxiety on presence has been suggested [63], and also has been highlighted the importance of emotional responses in presence [64]. Peperkorn et al. [62] analyzed the temporal dynamics in the interplay of presence-anxiety, and whether this relationship may change over the course of VRET trials. They found that, initially, presence influenced fear, suggesting a causal role for presence in the experience of fear in early stages of VRET. However, presence and fear were mutually dependent over time, and a reciprocal dependency was found between the two as VRET continued. High immersion and high presence also seemed to be important during initial VRET sessions. This study also showed a relevant role of stereoscopy compared to monoscopy, in fearful participants. These results coincide with a meta-analysis [65] examining the effect of immersive system technology on presence: aggregating effect sizes of 83 studies, these authors concluded that technological immersion had a medium-sized effect.

In conclusion, although presence seems to be an important factor in inducing anxiety and fear and achieving a successful treatment outcome, more research is needed to better understand how these factors interact and clarify the causal relationship between presence and fear in VRET. As this relationship is better understood, it will probably influence virtual environment designs for therapeutic uses.

VR-based Exposure Therapy Enhancement

As mentioned above, exposure therapy has been shown to be efficacious in the treatment of anxiety disorders; however, there is still room for improvement, and several lines of research have been devoted to enhancing exposure therapy outcomes by means of pharmacological compounds or the modulation of behavioral parameters [66]. Enhanced therapeutic outcomes has been defined [67] as greater reductions in symptom severity, greater response rates at post treatment and follow-up assessments, significant improvement earlier in treatment, or treatment outcomes obtained in less time.

One way to increase therapeutic outcomes in exposure therapy is to use cognitive enhancers, medications that enhance the neurological circuitry of fear extinction and can augment the efficacy of exposure therapy. For example, D-cycloserine (DCS) enhances fear extinction because it is a partial agonist of the glutamatergic N-methill-D-aspartate (NMDA) receptors. DCS is the most widely tested cognitive enhancer, but others have been used to support exposure

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therapy: yohimbine hydrochloride (YHCL), glucocorticoids and cortisol (G-CORT), and brain-derived neurotrophic factor (BDNF). The results indicate that cognitive enhancers can improve therapeutic outcomes in exposure therapy, with within-session fear habituation and between-session fear learning being key issues in enhancing fear extinction or, by contrast, reconsolidating existing fear memories. In summary, cognitive enhancers can be a safe and easy option to increase the effects of exposure therapy (for more information, see [67, 68, 69•].

Using VR can be a good option in studies where it is important to explore the processes and mechanisms involved in exposure therapy. When the target is testing a specific effect (e.g., to expedite treatment gains), it is important to have complete control over the variables involved in the exposure process, and VR can be an excellent choice (provides complete control over the cues presented and related parameters such as time, distance, size, etc.). Therefore, it is not surprising that some studies exploring the utility of cognitive enhancers have been conducted using VR. Specifically, two studies [70, 71] tested the utility of DCS in the treatment of acrophobia. Two other studies tested the use of other cognitive enhancers in specific phobias, YHCL in aerophobia [72], and G-CORT in acrophobia [73].

The second line of research focused on the enhancement of fear extinction through the modulation of behavioral parameters, such as multiple contexts, mass extinction, or concurrent exciters. Again, VR allows a highly controlled context manipulation, and it helps to induce contextual shifts during the VRET session. An interesting study [74••] explored the effects of multiple contexts in spider phobia using several VR contexts, and their results showed that multiple contexts enhance exposure therapy's generalizability. These results reveal the clinical utility of VR. If changing the context is important in exposure therapy, VR is an excellent option to expose patients to different contexts without leaving the consultation room. In in vivo exposure, shifting contexts would be more time consuming and costly.

Additionally, a further study [75] explored the differential role of perceptual versus conceptual cues (fear-related information) in fear activation/reduction in claustrophobia and spider phobia. Results showed that perceptual cues produced higher fear activation and greater fear habituation. These findings point to the potential of VR in controlling the manipulation of perceptual cues to enhance exposure therapy. These authors have also used VR to explore other features, such as fear reactivation prior to exposure therapy [76] or size estimation in spider phobia [77]. These studies found no effect of fear reactivation prior to exposure on treatment outcomes, and they showed that size estimation is biased in spider phobia, but this bias is corrected with exposure therapy.

In summary, VR is a good way to conduct exposure therapy, but also to study specific issues, such as pharmacological compounds and behavioral manipulations, that can enhance treatment outcomes.

Discussion and Conclusions

This review followed the structured PRISMA guidelines. Eleven studies were identified that fulfilled the selection criteria and contained potentially useful information about the efficacy of VRET for the treatment of phobias. As in previous meta-analyses [9, 10], the results further confirm VRET's potential in treating these problems. These studies have demonstrated that VR used in conjunction with traditional evidence-based psychological treatments can provide innovative treatment strategies for this problem.

However, some methodological issues should be taken into consideration. First, the sample sizes were small. This point was already highlighted [78], with the impact this may have on reaching erroneous conclusions [79, 80]. Second, there was a lack of studies carried out in clinical settings. All the studies were conducted in controlled research contexts, which makes it difficult to detect the degree of feasibility of VRET in natural clinical settings. Thus, it is necessary to carry out effectiveness and cost effectiveness studies in different delivery contexts (hospitals, private practices). The third issue is the data analysis. Statistical procedures that allow more precise investigations of mechanisms of change/causal mechanisms, such as multilevel regression analysis, are also lacking, although progress is already being made in this regard [22•]. Fourth, more attention should be paid to the CONSORT guidelines. As Table 2 reveals, only four studies provided a registration number, and only one study described how sample size was determined. Finally, it would be highly advisable for studies to report on dropouts and possible side effects.

Regarding the sociodemographic characteristics of participants, the majority were women and adult populations, then more studies with children and elderly populations are necessary. This could be due to the accessibility of the samples. In the case of children, in addition, there are ethical limitations because they require informed consent from parents, and the use of technologies is sometimes perceived as risky. However, paradoxically, children and the elderly are populations for which VR may be particularly useful because of the total control (and protection for participants) VR provide. In addition, in the case of children, a clear advantage is the possibility of incorporating aspects related to serious games (computerized games for serious purposes) and gamification (gaming elements used outside of games) that make it possible to design more attractive and engaging interventions [81]; although this might be true for all populations, in children it may be especially useful [82, 83]. Fortunately, some recent work [84•] stresses the importance of using VR to enhance children's lives by creating compelling experiences [84•, 85]. As for

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t2.1 **Table 2** CONSORT 2010 checklist

t2.2 Section/topic	Item no.	Checklist item	Studies including item (n = 11)
t2.3 Title and abstract			
t2.4	1a	Identification as a randomized trial in the title	8
t2.5	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	6
t2.6 Introduction			
t2.7 Background and objectives	2a	Scientific background and explanation of rationale	11
t2.8	2b	Specific objectives or hypotheses	9
t2.9 Methods			
t2.10 Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	8
t2.11	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	0
t2.12 Participants	4a	Eligibility criteria for participants	11
t2.13	4b	Settings and locations where the data were collected	8
t2.14 Interventions	5	The interventions for each group with sufficient details to allow r eplication, including how and when they were actually administered	9
t2.15 Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	4
t2.16	6b	Any changes to trial outcomes after the trial commenced, with reasons	0
t2.17 Sample size	7a	How sample size was determined	1
t2.18	7b	When applicable, explanation of any interim analyses and stopping guidelines	0
t2.19 Randomisation:			
t2.20 Sequence generation	8a	Method used to generate the random allocation sequence	9
t2.21	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
t2.22 Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
t2.23 Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
t2.24 Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	2
t2.25	11b	If relevant, description of the similarity of interventions	1
t2.26 Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
t2.27	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8
t2.28 Results			
t2.29 Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	11
t2.30	13b	For each group, losses and exclusions after randomisation, together with reasons	9
t2.31 Recruitment	14a	Dates defining the periods of recruitment and follow-up	4
t2.32	14b	Why the trial ended or was stopped	0
t2.33 Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	3
t2.34 Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11
t2.35 Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	9
t2.36	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	3
t2.37 Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	9

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t2.38 **Table 2** (continued)

	Section/topic	Item no.	Checklist item	Studies including item (n = 11)
t2.39	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	2
t2.40	Discussion			
t2.41	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	9
t2.42	Generalisability	21	Generalisability (external validity, applicability) of the trial findings	7
t2.43	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11
t2.44	Other information			
t2.45	Registration	23	Registration number and name of trial registry	4
t2.46	Protocol	24	Where the full trial protocol can be accessed, if available	4
t2.47	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	7

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older adults, as Grenier et al. [86] show, exposure therapy for late-life anxiety presents difficulties, and VR can be useful to overcome this obstacle. In any case, new published clinical protocols ensure the ongoing development of this research domain, applied to specific clinical conditions, such as dental [87] or spider phobia [88].

A second aim of this work was to identify possible relevant issues and challenges of VR in this field. Progress has been made in studying the possible relationship between presence and treatment outcomes. However, further research is still needed to obtain useful information about interactions and/or causal relationships that can guide us in developing new applications and in establishing guidelines for conducting VRET in clinical practice.

Moreover, several experimental studies have demonstrated the usefulness of VR in exploring hypotheses related to the processes and mechanisms involved in exposure therapy because of the high degree of control that this technology allows. In the same vein, several studies have shown that VR can be an excellent choice to study important factors related to fear activation/reduction in the lab, and to generate useful innovations for developing new treatment strategies to enhance therapeutic outcomes.

Technological advances, such as VR, entail new forms of human-machine interactions that may cause potential problems, and ethical issues should be taken into consideration. A major topic addressed two decades ago was cybersickness and after-effects of treatment due to the VR system itself. In those first years, there was also a concern about the appropriateness of utilizing VR in specific populations (e.g., PTSD, personality disorders, children, elderly population), and there has been no evidence of harmful effects of implementing a VR system. However, this does not mean that VR cannot lead to some kind of iatrogenic effect. Negative effects and deterioration can occur in VR just like in other psychological interventions. For instance, one study [89] focused on the negative effects among participants receiving Internet-based CBT and reported an average deterioration of 5.8 and 17.4% in the control conditions. These data are quite similar to those obtained in face-to face psychotherapy, and comparable to the deterioration rate (between 5 and 10%) reported by Lambert [90]. It would be extremely important to identify the extent to which VR treatments lead to deterioration.

It is also necessary to debate the direction that technological advances in the clinical field should take. Ongoing developments should be guided by a main principle, the personalization of health care. To do so, it is important to find out for whom certain applications can be more useful, in what contexts, and with what application specifications. These ideas coincide with other recent voices emphasizing the need to develop the next generation of VRET [91•] and reach the greatest number of people [92]. To accomplish this, it would be useful to combine several available technologies (e.g., VR, Internet, mobile devices, sensors, etc.) and "Big Data" possibilities [93]. Likewise, it is necessary to promote research in different cultural contexts, particularly in low-income countries where much less research is conducted, but even more psychological problems exist (e.g., [94]).

Finally, due to space limitations, other relevant themes have not been addressed. First, there is a possibility of using "virtual bodies and selves," virtual self-representations, and especially "autonomous doppelgangers" [95] to influence attitudes, emotions, and behavior. As Bailenson [96] points out, they will also allow us to have abilities that were not possible before. Researchers are just beginning to understand the implications and possibilities of these technologies. In the near

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future, these studies will provide many theoretical answers and practical applications for many fields, including phobia treatment, but this area of research also involves several ethical considerations that should be seriously considered. Second, studies have also investigated whether using technology such as VR can have a negative influence on the therapeutic alliance and, thus, on treatment outcomes. The data indicate that the relationship between patient and therapist are similar to what is observed in traditional face-to-face therapy. In any case, the recommendation would be to further explore this issue and use therapeutic alliance measures in clinical contexts where VRET is used, such as WAI-VAR [97].

This study has several limitations. First, no protocol was published to conduct this systematic review. Second, the authors of the studies were not contacted to obtain further information about ongoing, unpublished studies/manuscripts, and to complete some missing data from the primary studies that were not provided in the available articles. Finally, the quality assessment of primary studies was not reported study by study, but rather an overall table for CONSORT criteria is presented.

Conclusions

VRET applications have become an effective alternative that can equal the results of traditional treatments for phobias from an efficacy point of view. However, they are also tools capable of enhancing the psychological treatment field. In the coming years, there will be a significant increase in the routine use of these VRET applications in clinical contexts, but first there are important challenges to overcome. The most important is the acceptance of these technologies by clinicians. This acceptance will be associated with an additional reduction in costs, the development of easy-to-use devices, and the implementation of actions and programs to train the clinician. VR applications can be very useful for the treatment of phobias. In order to progress in this field, new research lines should find the best strategies to enhance exposure therapy, reduce the recurrence of fear, and increase the acceptability of exposure-based treatments. As stated above, VR applications are not a new form of therapy; however, they are a crucial element that can revolutionize the current Clinical Psychology field and contribute to creating a new portfolio of delivery models [92], helping us to "reboot" psychotherapy research and clinical practice and reduce the burden of mental illness.

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Compliance with Ethical Standards

Conflict of Interest Cristina Botella, Javier Fernandez-Álvarez, Verónica Guillén, Azucena García-Palacios, and Rosa Baños declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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AUTHOR PLEASE ANSWER ALL QUERIES.

Q1. Please check if the affiliations are presented correctly.
Q2. A temporary caption for Table 1 is provided. Kindly provide the appropriate caption for Table 1.
Q3. Please provide complete bibliographic details of this references [10, 20, 57, 66, 93].
Q4. References [62] and [65] based on original manuscript we received were identical. Hence, the latter was deleted and reference list and citations were adjusted. Please check if appropriate.
Q5. Please provide updated year.

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