The Use of Virtual Reality Technology in the Treatment of Anxiety and Other Psychiatric Disorders

Jessica L. Maples-Keller, PhD, Brian E. Bunnell, PhD, Sae-Jin Kim, BA, and Barbara O. Rothbaum, PhD

Learning objectives: After participating in this activity, learners should be better able to:

Evaluate the literature regarding the effectiveness of incorporating virtual reality (VR) in the treatment of psychiatric disorders
Assess the use of exposure-based intervention for anxiety disorders

Abstract: Virtual reality (VR) allows users to experience a sense of presence in a computer-generated, three-dimensional environment. Sensory information is delivered through a head-mounted display and specialized interface devices. These devices track head movements so that the movements and images change in a natural way with head motion, allowing for a sense of immersion. VR, which allows for controlled delivery of sensory stimulation via the therapist, is a convenient and cost-effective treatment. This review focuses on the available literature regarding the effectiveness of incorporating VR within the treatment of various psychiatric disorders, with particular attention to exposure-based intervention for anxiety disorders. A systematic literature search was conducted in order to identify studies implementing VR-based treatment for anxiety or other psychiatric disorders. This article reviews the history of the development of VR-based technology and its use within psychiatric treatment, the empirical evidence for VR-based treatment, and the benefits for using VR for psychiatric research and treatment. It also presents recommendations for how to incorporate VR into psychiatric care and discusses future directions for VR-based treatment and clinical research.

Keywords: anxiety disorders, exposure therapy, psychiatric treatment, technology, virtual reality

INTRODUCTION

Virtual reality (VR) is a technological interface that allows users to experience computer-generated environments within a controlled setting. This technology has been increasingly used in the context of mental health treatment and within

From the Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine (Drs. Maples-Keller and Rothbaum, and Mr. Kim); College of Nursing, Medical University of South Carolina (Dr. Bunnell).

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Correspondence: Jessica L. Maples-Keller, PhD, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, 12 Executive Park Dr. NE, Suite 200, Atlanta, GA 30329. Email: jessmaples@gmail.com

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clinical research. The primary focus of this article is to review the available literature on the effectiveness of VR in psychiatric treatment, with a specific emphasis on anxiety disorders. VR is well suited for use in exposure-based treatment for anxiety disorders as it provides the opportunity for a sense of presence and immersion in the feared environment. We will also discuss the potential advantages and disadvantages of using VR in psychiatric research and treatment, as well as practical recommendations for incorporating VR into psychiatric care.

VR aims to parallel reality and create a world that is both immersive and interactive.¹ Users fully experience VR when they believe that the paradigm accurately simulates the realworld experience that it attempts to recreate. The sense of presence, or "being there," in VR is facilitated through the use of technology such as head-mounted displays, gesture-sensing gloves, synthesized sounds, and vibrotactile platforms which allow for the stimulation of multiple senses and active exploration of the virtual environment.^{1–3} Some VR paradigms are programmed to react to the actions of the user. This dynamic interaction enables the user to engage with the VR environment in a more naturalistic and intuitive way.^{1,4} In all, VR is potentially a powerful tool for the psychiatric community because the user experience can be consistently replicated, tested, and modified within a safe environment. VR's precise

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control of sensory cues, particularly for auditory, tactile, and olfactory systems, increases the sense of realism and memory of the virtual environment.^{1,4,5}

Early development of what is now VR began in the 1950s and 1960s with several key inventions. In 1957, Morton Heilig invented the Sensorama, which aimed to engage all of the user's senses via specific components, such as smell generators and vibrating chairs, to provide a complete multisensory experience.⁵ In 1961, the Philco Corporation created Headsight, the first head-mounted displays to incorporate motion tracking and dual-monitor displays, for military training purposes.⁶ In 1965, Ivan Sutherland developed the Ultimate display, which employed the first computer-generated interface, thereby allowing users greater real-time interaction with VR.7 The concept of VR was eventually formalized in 1989 when Jaron Lanier coined the term virtual reality, at which point VR began to gain greater presence in research and psychiatric treatment.^{8,9} During the 1990s and early 2000s, psychologists began to utilize VR with prolonged exposure therapy. The first study to formally investigate the efficacy of VR-based exposure therapy (VRE) focused on treating acrophobia (fear of heights). Results suggested that VRE was effective,¹⁰ leading to additional studies on the use of VR-based therapy for anxiety disorders and other psychiatric conditions.

Anxiety Disorders

A wide body of research has suggested large treatment effects for exposure-based therapy for anxiety disorders.¹¹ Modern exposure therapy is based on emotion-processing theory, which posits that fear memories are structures that contain information regarding fear stimuli, responses, and meaning. As such, the goal of intervention is to activate and modify those fear structures by presenting novel incompatible information and facilitating emotion processing. VR-based techniques are ideal for exposure therapy, as the sense of presence experienced in VR provides the opportunity to immerse the patient in the feared environment that is tailored to match specific aspects of his or her fear structures, thereby activating those structures and enabling them to be modified. As such, the bulk of VR treatment research has been conducted for anxiety disorders, and results largely suggest that VRE is associated with large declines in anxiety symptoms,¹² is similar in efficacy to traditional exposure interventions, has a powerful real-life impact, and demonstrates good stability of results over time.¹³ Meta-analytic results for VRE for anxiety disorders even suggest a small effect size favoring VRE over in vivo conditions, even though most studies demonstrate no significant advantage when considered in isolation.¹⁴ Evidence suggests that treatment gains made in VRE generalize to real life, as meta-analytic results demonstrated that VRE patients, compared to wait-list patients, performed significantly better on behavioral assessments posttreatment, and demonstrated no significant differences compared to in vivo exposure patients at posttreatment and follow-up.¹⁵ As such, VRE is a promising treatment approach. The evidence for VRE will be reviewed not only for specific anxiety disorders but various other orders for which at least preliminary research has been conducted.

Advantages for Using VR for Psychiatric Research and Treatment

Within traditional exposure therapy, imaginal exposures are dependent on patients being able to effectively imagine specific feared stimuli. VR eliminates a potential barrier for patients who experience difficulty with imagining or visualization. In vivo exposures can be costly (e.g., an actual flight) or impractical to conduct (e.g., combat in Iraq or Afghanistan), whereas VR approaches allow for an inexpensive approach and the possibility of constructing exposures that may be difficult to implement in vivo. VRE provides the opportunity to manipulate exposures in ways that might not be possible in vivo, such as repeating, in VR, a flight landing multiple times. VRE also affords complete control, as the provider can control the dose and specific aspects of the exposure environment to match the specific patient's feared stimuli, and can also optimize individualized pacing through exposures. For instance, if a patient with the fear of flying is not ready for turbulence, the therapist can guarantee no turbulence. VR approaches allow for confidentiality to remain intact while conducting exposures, which may not be the case for in vivo exposures.

Findings show that patients report satisfaction with VR-based therapy and may find it more acceptable than traditional approaches. An early study on VRE for patients with posttraumatic stress disorder (PTSD) due to motor vehicle crashes demonstrated that patients reported very high satisfaction with VRE.¹⁶ In a sample of 150 patients with specific phobias, the refusal rate for VR exposure (3%) was lower than for in vivo exposure (27%),¹⁷ providing preliminary evidence that VR-based exposure may be more acceptable to patients. One study in a PTSD sample found equivalent satisfaction between VRE and imaginal exposure,¹⁸ while another found increased satisfaction for VRE.¹⁹ In a sample of 352 post-9/11 US soldiers, the majority reported that they would be willing to use most of the technology-based approaches for mental health care included in the survey (e.g., VR).²⁰ Additionally, 19% of those who reported that they would not be willing to talk to a counselor in person reported being willing to use VR approaches to access mental health care, suggesting VR may potentially address some barriers to treatment.

VR offers several advantages for conducting psychiatric research. The ability to control the exposure dose and stimulus presents the opportunity to conduct exquisitely controlled clinical and experimental research. For example, in the first human study examining the efficacy of combining D-cycloserine with exposure therapy,²¹ each research participant received exactly the same exposure to virtual heights. It is also feasible to collect other data relevant to treatment within VRE, such as psychophysiological assessment and data specific to the exposure (e.g., stimuli used, time in exposure). Important information regarding each particular disorder could also be collected. For example, in the case of substance use disorders, the exact timing of craving and decisions to use could be monitored in a VR environment. Additionally, testing of a skill or medication designed to reduce cravings could be tested in a VR environment rather than in the more dangerous "real world."

While VR provides many advantages, the disadvantages also need to be considered. In the past, both the technology itself and the costs were significant disadvantages in effort to disseminate VR in clinical settings. VR was difficult to set up, expensive, and unreliable-subject to malfunctions and other assorted problems.^{1,2,4,22} While the initial cost of VR continues to be a threshold problem, prices have decreased over time, and vendors have recently began selling smartphonebased VR therapy systems for as little as \$600. While the technology has improved-malfunctions are less likely, and the programs are more user-friendly^{4,23}—the possibility of technical glitches of one kind or another remains a potential disadvantage in clinical practice. Along these same lines, another potential disadvantage is the need for in-depth training and practice with VR prior to clinical use, to ensure the ability to effectively troubleshoot problems while still maintaining competent clinical care.

Treatment Course for VRE

VR-based exposure therapy follows the same sort of course as typical treatments, merely substituting VR for some other exposures or practices. VRE typically begins with 2–3 initial sessions that cover the following: psychoeducation regarding the specific disorder; psychosocial history; an overview of avoidance and the rationale for exposures; and the process of VR-based exposures. During this introductory period many VRE treatments also include some relaxation or coping strategies, such as breathing or relaxation exercises or cognitive restructuring. Typically, all subsequent sessions include conducting a VR exposure in which the patient progresses at an individualized pace through a graded exposure hierarchy.

Quality VRE is individualized to the patient. For instance, each step on the hierarchy can be repeated until patients' anxiety decreases significantly, as noted by the patient's subjective rating of distress and by the therapist's own observations. Progressing through the hierarchy should be a collaborative approach in which the therapist discusses each step with the patient before they move on to the next step in the graded exposure. The content available for a fear hierarchy is often preselected for VR exposures, as specific VR system content is developed for specific disorders and specific traumatic experiences or fears. Thorough assessment of the patients' fear or specific traumatic experience should occur prior to exposure in order to individualize both how they progress through the steps of the hierarchy and the time spent with different content. For instance, the fear-of-flying hierarchy includes eight steps, from walking through an airport terminal to flying during a thunderstorm with turbulence. For a patient with panic and agoraphobia, taxiing and takeoff may be an

important focus of treatment, with a focus on specific stimuli linked to these symptoms (e.g., the sound of the cabin door closing). By contrast, for a patient with specific phobia of flying that is due to an underlying fear of the plane crashing, flying through a thunderstorm and turbulence may be an important focus. For patients with PTSD, a thorough assessment of the patient's index trauma will facilitate the therapist's being able to prepare in advance the particular VR program (e.g., Virtual Iraq) and the specific setting and stimuli (e.g., time of day, specific weapon noises) to be used.

In a quality VR exposure, the therapist will effectively engage the patient in activating the fear structure. Therapists need to encourage and facilitate emotional engagement within VR and to discuss, as appropriate, how to work around any safety or similar behaviors. Specifically, since patients may attempt to engage in safety behaviors (e.g., repeating a specific mantra during takeoff in virtual flight), distraction, or active coping strategies during VR-based exposures, the therapist should review the rationale for exposure, emphasize the importance of not engaging in such behaviors, and help the patient to emotionally engage during the exposures.

METHOD

We now turn to a review of the available literature regarding the effectiveness of incorporating VR into the treatment of various psychiatric disorders, with a specific focus on exposurebased intervention for anxiety disorders. Systematic searches were conducted using PsycINFO, MEDLINE, EMBASE, and Google Scholar. Search terms included virtual reality, virtual reality exposure therapy, computer-generated exposure, virtual reality with psychiatric, therapy, psychological, anxiety, disorder, specific phobia, social anxiety disorder, posttraumatic stress disorder, panic, agoraphobia, generalized anxiety disorder, obsessive compulsive disorder, schizophrenia, psychosis, pain, addiction, eating disorder, bulimia, anorexia, binge eating, and autism. We identified studies mentioning VR-based psychiatric treatment in the title, abstract, or keywords. The most recent search was in September 2016. We included studies that enrolled patients with a psychiatric condition who received VR-based intervention. We excluded studies that did not present measurements of treatment outcomes. Given that many VR-based approaches are relatively novel or preliminary, we did not require studies to be randomized (or quasi randomized) and controlled.

RESULTS

Specific Phobias

Specific phobia (SP) is characterized by marked fear/anxiety relating to a specific object or situation (e.g., flying, heights, animals, needles, or blood).²⁴ SPs, particularly flight phobia, are among the most researched disorders within the scope of VR-based interventions. Two studies on fear of flying using a within-group design have demonstrated significant reductions in flight-related anxiety²⁵ and also an increased likelihood to fly on an airplane following treatment.²⁶ Several

randomized, controlled trials (RCTs) of VR-based exposure have demonstrated symptom reduction and behavioral change (e.g., decreased avoidance) superior to control conditions and equivalent to that of cognitive-behavioral therapy (CBT) alone.^{23,27–32} Further investigation revealed that these treatment gains were maintained one^{33,34} and three³⁵ years posttreatment. Additional studies have found that VRE for fear of flying may be enhanced by the inclusion of physiological feedback³⁶ and motion simulation.³⁷ VRE has shown acceptability and efficacy in the treatment of other SPs. In particular, VR is effective in treating acrophobia based on both within-group,³⁸ and controlled between-group, data.^{10,39,40} Similar effects have been observed in RCTs for treating arachnophobia (fear of spiders)^{41–43} and, in one multiple-baseline study, fear of driving.⁴⁴

In summary, numerous studies have shown efficacy for VR-based CBT for the treatment of SPs. Many of these studies have used RCTs with adequate sample sizes and have found large treatment effects both within and between treatment groups. Some have incorporated behavioral-avoidance tests to the actual feared stimulus and have demonstrated meaningful behavioral change. Further, data suggest that treatment gains are maintained for years following treatment completion. The cumulating data showing efficacy of VRE for SPs are promising, particularly for patients with fears pertaining to situations for which in vivo treatment may not be safe, cost-effective, or feasible.

Social Anxiety Disorder

Social anxiety disorder (SAD) is a psychiatric condition in which the patient experiences anxiety in social interactions (e.g., conversations, meeting new people, public speaking) during which they might be judged or socially evaluated by others.²⁴ VR-based interventions for SAD typically involve the use of computer-generated social environments (e.g., classrooms, auditoriums, conference rooms) with virtual audiences. In examining generalized SAD, two RCTs found VR-based CBT to be as effective as traditional CBT⁴⁵ and superior to control conditions.⁴⁶ VR-based CBT for fear of public speaking has demonstrated effects similar to traditional CBT and above that of controls,^{47–49} and effects were maintained one year posttreatment.^{47,50} Finally, preliminary data have begun to show efficacy for VR in treating school-based anxiety, including test anxiety.^{51,52}

Although fewer studies have examined the effects of VRE for SAD than for SPs, the data thus far have been encouraging. VR can be especially useful for this population, as finding multiple confederates with whom a patient can interact can be costly and time-consuming. Given these data and the potential cost savings of using VR-based social interactions, VR can be a particularly useful adjunct to CBT for SAD.

Posttraumatic Stress Disorder

PTSD involves a history of exposure to a traumatic event and also symptoms of intrusion, avoidance, negative alterations in

cognitions and mood, and alterations in arousal and reactivity.²⁴ Across several studies, VRE for PTSD demonstrates a medium-to-large treatment-effect size,¹³ superior treatment outcomes compared to wait-list controls, and outcomes comparable to standard exposure treatment.53 Early case studies54-56 and open-trial designs across a broad range of traumatic experiences^{16,57,58} suggested that this treatment approach held promise for treating PTSD. A preliminary study comparing VR-based exposure therapy for PTSD following the World Trade Center attacks found that the VR group (n = 13) demonstrated a significant decline in PTSD scores compared to the wait-list group (n = 8) and that this improvement was maintained at a sixmonth follow-up assessment.⁵⁹ Results demonstrated statistical and clinical significance: baseline scores in both groups fell within the severe range, whereas at posttreatment the mean score for the VR group was in the mild range, and seven of the ten VR completers did not meet PTSD diagnostic criteria. No significant effect was identified for depressive symptoms or general distress, but these scores were relatively low at baseline for both groups. The sample in this study was not demographically diverse (i.e., mostly middle-aged men), but the participants' exposure to the attacks did vary (i.e., firefighters, disaster workers, and civilians), suggesting that the standardized virtual stimuli were able to effectively engage individuals with diverse experiences of the traumatic event.

In the first investigation to compare VRE to another active treatment, Vietnam veterans were randomly assigned to VRE or present-centered therapy.⁶⁰ Results did not identify a significant difference posttreatment but did identify a moderate advantage of VRE six months posttreatment. Notably, the sample size was small (n = 11), indicating the need for larger trials with sufficient power to detect treatment differences. Open trials have provided further support for using VRE for PTSD for combat-related PTSD,^{61,62} and a small RCT comparing VRE to treatment as usual for active-duty personnel with combat-related PTSD found VRE to be more effective as determined by posttreatment PTSD symptoms.⁶³ A recent study of 156 post-9/11 veterans investigated VRE augmented with D-cycloserine or alprazolam compared to placebo for military-related PTSD.⁶⁴ Results suggested no overall differences related to medication use, but six sessions of VRE significantly improved PTSD symptoms and psychobiological measures of startle and cortisol reactivity at posttreatment and at 3, 6, and 12 months posttreatment, suggesting that VRE for PTSD produced clinical improvement that is sustained over time. It is notable that VR-based standardized stimuli has been used for psychophysiological assessment both before and after PTSD treatment.⁶⁴

In a randomized, double-blind trial, D-cycloserine or placebo was administered prior to VR exposure treatment sessions for patients with chronic PTSD (n = 25).⁶⁵ Both groups demonstrated significant decreases in PTSD symptoms at posttreatment, and the group that received D-cycloserine demonstrated significantly higher remission rates at posttreatment and significantly higher remission rates and lower PTSD scores at a six-month follow-up assessment. The VR/D-cycloserine group demonstrated greater improvement in depressive symptoms and state anger at six-month follow-up. These findings suggest that VR exposure therapy for PTSD is effective and may be enhanced by D-cycloserine. One recent study randomly assigned 162 active-duty soldiers to ten sessions of prolonged exposure, VRE, or minimal-attention wait-list.⁶⁶ At posttreatment, both VRE and prolonged exposure resulted in greater improvement, with no significant differences between the treatment groups. Contrary to hypotheses, prolonged exposure demonstrated a greater improvement than VRE at three- and six-month follow-ups. These results suggest that the prolonged exposure may provide better symptom recovery, over time, than VRE. The authors suggest that individuals may vary in how activated they are by VR environments and that improved VRE content may assist in emotional engagement. While the current literature on VR exposure treatment for PTSD suggests promise, it is notable that many of the studies use small samples, do not employ randomization, or lack a comparison to an active treatment condition, suggesting that future research would benefit from more randomized clinical trials with larger samples and comparison to existing standard-of-care treatment, such as traditional prolonged exposure therapy.

Panic Disorder and Agoraphobia

Panic disorder and agoraphobia (PDA) are characterized by a sudden rush of anxiety manifested by physiological (e.g., heart palpitations, sweating, choking sensations) and cognitive (e.g., racing thoughts, fear of dying) symptoms, leading to fear or avoidance of specific places or situations.²⁴ VRE for PDA presents situations that commonly elicit panic attacks such as tunnels, parking lots, city squares, and highways. Early data that made use of multiple-baseline designs found initial support for the use of VR in treating PDA.⁶⁷ Although RCTs generally have found positive effects for VRE for PDA, studies have varied regarding the differences between VRE and traditional exposure therapy. Most studies have found VRE to be as effective as traditional exposure therapy in ameliorating PDA symptoms. Findings from some investigations suggest that VRE may result in better treatment response^{68,69} and in fewer required treatment sessions⁷⁰ but that it may not differ from traditional exposure therapy,⁷ particularly when considering long-term outcomes. The potential implication is that any incrementally better effects may appear early on in treatment.⁶⁸ The equivalent, longerterm treatment effects of VRE versus traditional approaches have remained stable for 3,⁶⁸ 6,⁷² 9,⁷³ and 12 months⁷⁴ posttreatment. Altogether, investigations of VR-based exposure for PDA using rigorous study design and methodology support the efficacy of these tools for treating PDA. Moreover, VR-based CBT for PDA has several advantages, including improved treatment response and decreased time required for treatment.

Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is a condition in which the patient experiences persistent, excessive, and intrusive worrying to the extent that daily functioning becomes difficult.²⁴ Gorini and colleagues⁷⁵ conducted a small-scale RCT (n = 20) using VR in conjunction with biofeedback for patients to practice relaxation exercises during treatment. Patients were randomly assigned to VR with biofeedback, VR without biofeedback, or wait-list control condition. Although the study did not have enough power to examine betweengroup differences, it provides preliminary support for the feasibility of using VR for patients with GAD. Thus far, this study has been the only one to examine the use of VR in treating GAD. The dearth of studies may be due to the difficulty associated with creating standardized VR scenarios that are able to capture the numerous, varying, individualized worries of patients with GAD. Given this complication, VR-based treatment programs could focus on some of the more common worries among patients with GAD (e.g., health anxiety, something happening to a loved one). Alternatively, or if a patient's worries are not readily addressable with such scenarios, VR-based treatment could serve as a visual guide for breathing exercises and for practicing relaxationor mindfulness-based approaches.

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD) is marked by intrusive thoughts, images, or impulses that cause anxiety (e.g., fear of contamination, need for symmetry) and lead to compensatory repetitive behaviors (e.g., excessive cleaning, arranging things in a specific way) that reduce anxiety. Thus far, no RCTs have assessed the efficacy of VR in treating OCD, although two studies have examined the ability of VR to elicit anxious responding in patients with OCD.^{76,77} Data from those studies suggest that VRE to feared stimuli was able to elicit anxiety in patients with OCD relative to controls (with no diagnosis). Further, participants' level of anxiety was positively associated with their immersion, the extent to which they felt that they were physically present in the virtual environment. This result suggests a need for VR scenarios to be realistic and relevant to the patient's concerns. Similar to GAD, the impetus for obsessions and compulsions varies across patients, making it difficult to develop all-encompassing VR programs that meet the needs of all patients. Further, many patients have numerous obsessions and associated compensatory behaviors, which adds to the complications. VR may not be necessary, however, for OCD, as many of the feared stimuli may be readily accessible in the environment (e.g., toilets) or patients' imaginations (e.g., making a mistake). Despite these difficulties, using VR during the treatment of OCD may be advantageous for patients whose obsessions are not feasible or appropriate for traditional exposure therapy (e.g., exposure to public restrooms). Give that data for VR-based CBT for OCD are preliminary but promising, more research in this area is warranted.

Schizophrenia

While the preponderance of research investigating the use of VR in psychiatric care has focused on anxiety disorders, this treatment approach has demonstrated promise in treating other disorders. Schizophrenia is a severe mental illness that includes psychotic symptoms (e.g., hallucinations, delusions), disruptions to normal emotional/behavioral functioning (e.g., flat affect, reduced pleasurable experiences, isolation), and difficulty with cognitive processing.²⁴ Data examining VR as an adjunct to treatment in this population have been limited, but initial investigations have been promising. VR scenarios used in treating schizophrenia have included social situations during which patients have practiced social skills and learned to cope with social distress associated with delusional convictions. One small RCT found that combining VR-based social interactions with exposure and cognitive therapy led to decreases both in persecutory delusions and in distress during in vivo social interactions.⁷⁸ Three studies have used VR as an adjunct to social-skills training (SST) for schizophrenic patients, two of which were uncontrolled pilot investigations that provide preliminary support for the efficacy of this approach in improving social skills and interactivity.^{79,80} Another RCT of 91 schizophrenic individuals found that in comparison to traditional SST, SST with VR components resulted in increased interest in SST, in generalization of skills learned during treatment, and in improved ability to converse and be assertive, although patients receiving traditional SST demonstrated better nonverbal social skills.⁸¹ The existing data are limited, but these preliminary results are promising, particularly given the above-mentioned barriers to providing exposure to social interactions.

Acute and Chronic Pain

Given that the experience of pain requires conscious attention, cognitive distraction is often incorporated as part of pain management in an attempt to shift attention and focus away from painful medical procedures. VR has been studied as a way to facilitate distraction from acute pain during painful procedures, such as burn-related pain or physical therapy. An initial investigation for a small sample of four burn patients found that subjective pain ratings were lower when patients were in VR during occupational therapy.⁸² A subsequent case study in a pediatric cancer patient provided further support that VR distraction may be useful in decreasing pain during painful medical procedures.⁸³ A within-subjects randomized trial comparing routine analgesia and routine analgesia combined with a VR game found the latter to be significantly more effective in reducing pain responses for children undergoing burn treatment.⁸⁴ A controlled trial comparing VR to other distraction techniques found that VR was more effective than some distraction techniques (i.e., child care worker, music, TV with headphone) in reducing subjective pain severity, but VR was not significantly more effective than watching television.⁸⁵ In an fMRI study investigating the impact of VR on pain-related brain activity, participants subjectively reported decreased time thinking about pain and decreased pain severity, and demonstrated significantly reduced activity in brain regions related to both sensory and emotional pain processing, providing subjective and objective support that VR techniques can aid in pain reduction.⁸⁶

VR has also been used to help individuals with chronic pain learn and practice pain-management techniques in combination with existing cognitive or behavioral interventions, as VR may help nonresponders to conventional treatment and can provide the ability to standardize instructions and stimuli.⁸⁷ A VR system for chronic-pain populations has been developed in which patients take a virtual meditative walk to learn mindfulness-based stress reduction; preliminary results suggest that this system is more effective than non-VR mindfulness in reducing subjective pain.88 A study of patients with fibromyalgia found that using VR with activity-management treatment—which included VR-based sessions involving activity-management instructions, motivation enhancement, overcoming activity-related barriers, and acknowledgment of personal strengths-was significantly more effective than treatment as usual in improving functional disability.⁸⁹

In sum, findings suggest that for short-term, acute pain during medical procedures, VR added to standard pharmacological pain management can be more effective than standard analgesia alone in reducing subjective pain severity. While this result presumably relates to cognitive distraction, specific mechanisms are currently unknown,⁹⁰ and future research could investigate mechanisms underlying this effect. Preliminary evidence also suggests that VR may be helpful in helping individuals with chronic pain learn and practice specific pain-management techniques, such as mindfulness or activity management.

Addiction

Conditioned reactivity to drug-related cues is an important maintenance factor in drug and alcohol addiction, and in order to prevent relapse, repeated exposure to drug-related cues has been used to reduce cue-reactive craving. VR cue exposure provides the opportunity to conduct repeated exposures to drug-related cues in a controlled therapeutic environment. An initial pilot study found that VR-based cue exposure (e.g., a virtual bar, syringe, needle) was effective at eliciting physiological arousal, subjective craving, and urges to use drugs in men with opioid dependence.⁹¹ Another investigation found that a VR crack-cocaine environment was effective at eliciting craving and physiological arousal in a sample dependent upon crack cocaine.⁹² A VR casino environment was shown to be effective in eliciting psychophysiological arousal and urges to gamble in a sample of recreational gamblers,⁹³ suggesting that VR-based, cue-elicited craving is effective across different addiction populations. In a nicotine-dependent sample, a VR-based smoking environment elicited, compared to a neutral cue, increased psychophysiological arousal and craving-a response that then decreased over the course of a four-week treatment using VR cue exposure.⁹⁴ In a sample of nicotine-dependent cigarette smokers, self-reported

withdrawal symptoms and craving prior to a VR cue exposure were predictive of craving experienced in VR, and significant increases in heart rate were present for three of the four VR smoking cues, providing further support for the ability of VR stimuli to effectively elicit subjective craving and physiological arousal related to substance-related cues.⁹⁵ A double-blind placebo study investigated the effects of D-cycloserine in concurrent cocaine- and nicotine-dependent participants (n = 29)who engaged in VR based cue-exposure therapy in conjunc-tion with brief CBT for smoking.⁹⁶ Although results indicated no significant effect of D-cycloserine, overall significant decreases in smoking, craving for cigarettes, and cue-induced cravings were observed. Notably, approximately 90% of the treatment sessions were attended, suggesting that VR-based cue-exposure therapy is a tolerable treatment approach. A randomized trial of CBT plus either smoking VR cue-exposure therapy or placebo VR cue-exposure therapy found that the smoking VR participants had a higher quit rate and reported significantly fewer cigarettes smoked per day at the end of treatment.⁹⁷ As such, the current literature suggests that VR-based environments are effective at eliciting cue reactivity and craving in different substance-dependent populations and can be effectively incorporated within repeated cueexposure treatment.

Eating Pathology

VR approaches have been used with different forms of eating pathology to address body-image disturbances and eating, shape, and weight concerns. VR has been used to explore and challenge body-image distortions, to implement exposure to food cues in order to identify and challenge eating, shape, and weight concerns, and to practice more effective eating strategies. An early investigation used several different VR environments, including household rooms with food items, to explore patients' eating, shape, and weight beliefs and concerns, and also used images of different body types to resolve discrepancies in patients' perceptions of their bodies.⁹⁸ The results lent preliminary support that these approaches improved body awareness in obese patients and those with binge-eating disorders.⁹⁸ A follow-up, controlled investigation of 28 obese patients randomized to VR treatment or CBT-based groups found that VR treatment resulted in significantly greater improvements with body satisfaction, anxiety level, and problematic eating.⁹⁹ No significant differences were found for self-efficacy or stages of change in psychotherapy across the two groups. In a randomized trial with 13 eating-disordered patients comparing VR-based CBT for body-image disturbances to traditional CBT, VR-based CBT was found to result in significantly greater symptom improvement in body-image disturbances; no differences were found for eating-disorder symptoms across the two groups.¹⁰⁰ In a controlled study comparing CBT for eating disorders with and without a component of VR-based body-image treatment, the VR group demonstrated greater improvement at posttreatment and one-month follow-up; it is notable, however, that the VR

group received additional treatment sessions.¹⁰¹ As such, the current literature provides preliminary support for the efficacy of incorporating VR into the treatment of different types of eating pathology and weight problems; results suggest that VR may result in treatment effects comparable to traditional CBT approaches and may result in greater improvement for some specific outcomes.

Autism

Autism spectrum disorder (ASD) is a developmental disorder marked by repetitive or restrictive patterns of behavior and by difficulties with social communication and interaction. Research on the effectiveness of VR in treating ASD suggests preliminary support for social improvement. Lahiri and colleagues¹⁰² found evidence for using a VR-based computer task to improve social-communication performance in autistic teenagers. The applicability of the results is questionable, however, because of the study's sample size and its proof-ofconcept design. Sample size was small (n = 8), and the range of ASD severity was limited. The researchers enrolled only autistic teenagers with average or above-average intelligence because the task utilized a menu-driven communication system that required a certain level of reading ability-consequently limiting the sample's representativeness. Intervention studies have shown relative improvements with regard to theory of mind, emotion recognition, and communication skills.^{103,104} All of the studies mentioned demonstrate low dropout rates and suggest VR's high acceptability to VR.¹⁰²⁻¹⁰⁴ Overall, the preliminary evidence indicates that VR could be feasibly and effectively incorporated into psychiatric treatment for ASD.

RECOMMENDATIONS FOR HOW TO INCORPORATE VR INTO PSYCHIATRIC CARE

VR is incorporated at the point in treatment when in vivo exposure would otherwise be administered. As an example, a typical protocol using VR for fear of flying teaches anxiety-management techniques in the first four sessions and incorporates VR exposure to a virtual airport and airplane in the last four sessions.²³ Specific equipment and training are needed to integrate VR into psychiatric practice effectively. AVR system will typically include a head-mounted display and a platform (for the patients) and a computer with two monitors—one for the provider's interface in which he or she constructs the exposure in real time, and another for the provider's view of the patient's position in the VR environment.

VR-specific training is an important consideration in integrating VR into psychiatric practice. VR vendors provide both Internet-based training courses in VR therapy and onsite, structured training on VR use within therapy. Providers should be sufficiently trained, including through role playing, to feel proficient with the VR technology before using it with patients. Training for providers should include information and practice on troubleshooting glitches within sessions and also possible contact information for individuals from the VR vendor who may be able to help troubleshoot.

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Additionally, providers should be well trained in the rationale for incorporating VR within psychiatric care, which would ensure that they are able to effectively communicate that rationale—and therefore the credibility of the treatment approach—to patients. Given that VR is most frequently used during exposure therapy for anxiety disorders, sufficient training in exposure therapy should be considered a prerequisite for integrating VR into patient care. Continued supervision and support in exposure therapy should also be in place. Bad VR therapy is still just bad therapy.

FUTURE DIRECTIONS FOR VR-BASED TREATMENT AND CLINICAL RESEARCH

The empirical literature suggests that VR demonstrates promise in treating psychiatric conditions and that clinical research with VR could make a potentially important contribution to patient care. A recent review of VRE RCTs, however, found that overall methodological rigor was low;¹⁰⁵ authors noted that recent research, rather than becoming more methodologically rigorous over time, has focused on preliminary support for novel uses for VR. Another review noted the continued use of small samples and no controls,¹⁰⁶ echoing the need for better-powered and controlled studies comparing VR-based treatment to other treatment approaches.

Future research could identify factors relevant to determining the best candidates for VR-based treatment. Individual differences related to immersion or sense of presence may be relevant. More broadly, research focused on the therapeutic process within VR—and not just on outcomes—will be important.¹⁰⁷ Research testing hypothesized mediators and moderators of VR-based treatment will prove informative for example, in investigating factors such as emotion processing, psychophysiological markers during exposure, and the therapeutic alliance.

When designing a VR study, the use of control conditions and large-enough sample sizes is essential. Studies need to be sufficiently powered to detect significant effects while taking into account dropout rates during treatment and attrition during the follow-up period. The initial clinical assessments should include standardized, semistructured diagnostic interviews administered by trained mental health professionals. Any comorbid conditions also need to be noted. Additionally, it would be beneficial to assess patients' expectancies regarding outcomes, their baseline psychophysiological responses to standardized relevant VR stimuli, and personality and other individual differences that could be hypothesized to relate to the ability to experience presence/immersion at baseline. Information on current psychoactive medications use should be collected, and participants would ideally agree to stay on the same dose throughout the course of the study and follow-up assessments. Therapists should document the following: patients' subjective ratings of distress ratings during each VRE session; the record from psychophysiological monitoring during exposure; therapist and patient ratings of therapeutic alliance; patients' engagement/presence/immersion

during exposure; and patients' global improvement. The therapist can also document the amount of time spent in VR, the repetitions of the exposure, and the specific VR environments and cues used. It is recommended that therapy sessions be video- or audio-recorded to facilitate investigation of process variables or behavioral coding. Posttreatment assessments should ideally occur over a follow-up period of at least 12 months, to allow for the investigation of the treatment effects over time. Posttreatment assessment could include multiple indicators of treatment outcome, including patient report, blind-assessor report, therapist report, behavioral tasks, and quality-of-life assessment. Methodologically rigorous and controlled use of VR within clinical research can help improve and elucidate the treatment process, processes related to anxiety, and fear processes more broadly-and potentially advance the move toward personalized medicine.

CONCLUSIONS AND SUMMARY

Conventional wisdom is that it takes about 20 years from the time the first research is published to becoming common use. The first study using VR to treat a psychological disorder was published in 1995,¹⁰ and here we are 20 years later! VR has emerged as a viable tool to help in a number of different disorders, with the most strength of evidence for use in exposure therapy for patients with anxiety disorders, cue exposure therapy for patients with substance use disorders, and distraction for patients with acute pain requiring painful procedures. Overall, meta-analyses have indicated that VR is an efficacious tool, compares favorably to existing treatments, and has lasting effects that generalize to the real world. Problems have been noted in the existing research, however, including small sample sizes, lack of methodological rigor, and lack of comparison groups. With the cost of head-mounted displays coming down and with smaller smartphone applications being developed, it is likely that VR applications will proliferate. It will be important that these are treated as tools and that therapists are properly trained in their applications.

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REFERENCES

- 1. Rizzo AA, Buckwalter JG, Neumann U. Virtual reality and cognitive rehabilitation: a brief review of the future. J Head Trauma Rehabil 1997;12:1–15.
- 2. Rothbaum BO, Hodges L, Kooper IR. Virtual reality exposure therapy. J Psychother Pract Res 1997;6:219–26.
- 3. Brooks FP. What's real about virtual reality? IEEE Comput Graph Appl 1999;19:17–27.
- 4. Anderson PL, Rothbaum BO, Hodges L. Virtual reality: using the virtual world to improve quality of life in the real world. Bull Menninger Clin 2001;65:78–91.

- Dinh HQ, Walker N, Song C, Kobayashi A, Hodges LF. Evaluating the importance of multi-sensory input on memory and the sense of presence in virtual environments. In: Rosenblum L, Astheimer P, Teichmann D, eds. Proceedings: IEEE virtual reality 1999 (Los Alamitos, CA: IEEE Computer Society, 1999):222–8. http://ieeevr.org/2016/past-conferences/
- 6. Comeau C, Bryan J. Headsight television system provides remote surveillance. Electron 1961;34:86–90.
- 7. Sutherland IE. The ultimate display. In: Proceedings of the International Federation for Information Processing Congress 1965. Vol. 2.: 506–8. http://worrydream.com/refs/Sutherland %20-%20The%20Ultimate%20Display.pdf
- 8. Gorini A, Riva G. Virtual reality in anxiety disorders: the past and the future. Expert Rev Neurother 2008;8:215–33.
- 9. Lanier J, Minsky M, Fisher S, Druin A. Virtual environments and interactivity: windows to the future. Comput Graph (ACM) 1989;23:7–18.
- Rothbaum BO, Hodges LF, Kooper R, Opdyke D, Williford JS, North M. Effectiveness of computer-generated (virtual reality) graded exposure in the treatment of acrophobia. Am J Psychiatry 1995;152:626–8.
- 11. Bandelow B, Reitt M, Rover C, Michaelis S, Gorlich Y, Wedekind D. Efficacy of treatments for anxiety disorders: a meta-analysis. Int Clin Psychopharmacol 2015;30:183–92.
- 12. Parsons T, Rizzo AA. Affective outcomes of virtual reality exposure therapy for anxiety and specific phobias: a metaanalysis. J Behav Ther Exp Psychiatry 2008;39:250–61.
- 13. Opriș D, Pintea S, García-Palacios A, Botella C, Szamosközi Ş, David D. Virtual reality exposure therapy in anxiety disorders: a quantitative meta-analysis. Depress Anxiety 2012;29:85–93.
- 14. Powers MB, Emmelkamp PMG. Virtual reality exposure therapy for anxiety disorders: a meta-analysis. J Anxiety Disord 2008;22:561–9.
- 15. Morina N, Ijntema H, Meyerbroker K, Emmelkamp PMG. Can virtual reality exposure therapy gains be generalized to real-life? A meta-analysis of studies applying behavioral assessments. Behav Res Ther 2015;74:18–24.
- Beck JG, Palyo SA, Winer EH, Schwagler BE, Ang EJ. Virtual reality exposure therapy for PTSD symptoms after a road accident: an uncontrolled case series. Behav Ther 2007;38:39–48.
- 17. Garcia-Palacios A, Botella C, Hoffman H, Fabregat S. Comparing acceptance and refusal rates of virtual reality exposure therapy vs. in vivo exposure by patients with specific phobias. Cyberpsychol Behav 2007;10:722–4.
- De la Rosa A, Cárdernas-López G. Posttraumatic stress disorder: efficacy of a treatment program using virtual reality for victims of criminal violence in Mexican population. Anu Psicología 2012;42:377–91.
- Baños ŘM, Botella C, Guillen V, et al. An adaptive display to treat stress-related disorders: EMMA's world. Br J Guid Counc 2009;37:347–56.
- Wilson J, Onorati K, Mishkind M, Reger M, Gahm GA. Soldier attitudes about technology-based approaches to mental healthcare. Cyberpsychol Behav 2008;11:767–9.
- 21. Ressler KJ, Rothbaum BO, Tannenbaum L, et al. Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinction of fear. Arch Gen Psychiatry 2004;61:1136–44.
- 22. Rothbaum BO, Hodges LF, Kooper R, Opdyke D, Williford JS, North M. Virtual reality graded exposure in the treatment of acrophobia: a case report. Behav Ther 1995;26:547–54.
- 23. Rothbaum BO, Hodges L, Smith S, Lee JH, Price L. A controlled study of virtual reality exposure therapy for the fear of flying. J Consult Clin Psychol 2000;68:1020–6.
- 24. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing, 2013.

- Ferrand M, Ruffault A, Tytelman X, Flahault C, Négovanska V. A cognitive and virtual reality treatment program for the fear of flying. Aerosp Med Hum Perform 2015;86:723–7.
- Kahan M, Tanzer J, Darvin D, Borer F. Virtual reality–assisted cognitive-behavioral treatment for fear of flying: acute treatment and follow-up. Cyberpsychol Behav 2000;3:387–92.
- Krijn M, Emmelkamp PMG, Ólafsson RP, et al. Fear of flying treatment methods: virtual reality exposure vs. cognitive behavioral therapy. Aviat Space Environ Med 2007;78: 121–8.
- 28. Maltby N, Kirsch I, Mayers M, Allen GJ. Virtual reality exposure therapy for the treatment of fear of flying: a controlled investigation. J Consult Clin Psychol 2002;70:1112–8.
- 29. Mühlberger A, Herrmann MJ, Wiedemann G, Ellgring H, Pauli P. Repeated exposure of flight phobics to flights in virtual reality. Behav Res Ther 2001;39:1033–50.
- 30. Rothbaum BO, Anderson P, Zimand E, Hodges L, Lang D, Wilson J. Virtual reality exposure therapy and standard (in vivo) exposure therapy in the treatment of fear of flying. Behav Ther 2006;37:80–90.
- Tortella-Feliu M, Botella C, Llabrés J, Bretón-López JM, del Amo AR, Baños RM. Virtual reality versus computer-aided exposure treatments for fear of flying. Behav Modif 2011;35: 3–30.
- 32. Triscari MT, Faraci P, Catalisano D, D'Angelo V, Urso V. Effectiveness of cognitive behavioral therapy integrated with systematic desensitization, cognitive behavioral therapy combined with eye movement desensitization and reprocessing therapy, and cognitive behavioral therapy combined with virtual reality exposure therapy methods in the treatment of flight anxiety: a randomized trial. Neuropsychiatr Dis Treat 2015;11:2591–8.
- 33. Rothbaum BO, Hodges L, Anderson PL, Price L, Smith S. Twelvemonth follow-up of virtual reality and standard exposure therapies for the fear of flying. J Consult Clin Psychol 2002;70:428.
- Mühlberger A, Weik A, Pauli P, Wiedemann G. One-session virtual reality exposure treatment for fear of flying: 1-year follow-up and graduation flight accompaniment effects. Psychother Res 2006;16:26–40.
- 35. Wiederhold BK, Wiederhold MD. Three-year follow-up for virtual reality exposure for fear of flying. Cyberpsychol Behav 2003;6:441–5.
- 36. Wiederhold BK, Jang DP, Gevirtz RG, Kim SI, Kim IY, Wiederhold MD. The treatment of fear of flying: a controlled study of imaginal and virtual reality graded exposure therapy. IEEE Trans Inf Technol Biomed 2002;6:218–23.
- Mühlberger A, Wiedemann G, Weik A. Efficacy of a one-session virtual reality exposure treatment for fear of flying. Psychother Res 2003;13:323.
- Emmelkamp PMG, Bruynzeel M, Drost L, van der Mast CG. Virtual reality treatment in acrophobia: a comparison with exposure in vivo. Cyberpsychol Behav 2001;4:335–9.
- Emmelkamp PM, Krijn M, Hulsbosch AM, De Vries S, Schuemie MJ, van der Mast CA. Virtual reality treatment versus exposure in vivo: a comparative evaluation in acrophobia. Behav Res Ther 2002;40:509–16.
- 40. Krijn M, Emmelkamp PM, Biemond R, de Wilde de Ligny C, Schuemie MJ, van der Mast CA. Treatment of acrophobia in virtual reality: the role of immersion and presence. Behav Res Ther 2004;42:229–39.
- Garcia-Palacios A, Hoffman H, Carlin A, Furness TU, Botella C. Virtual reality in the treatment of spider phobia: a controlled study. Behav Res Ther 2002;40:983–93.
- 42. Michaliszyn D, Marchand A, Bouchard S, Martel MO, Poirier-Bisson J. A randomized, controlled clinical trial of in virtuo and in vivo exposure for spider phobia. Cyberpsychol Behav Soc Netw 2010;13:689–95.

Harvard Review of Psychiatry

- Shiban Y, Pauli P, Mühlberger A. Effect of multiple context exposure on renewal in spider phobia. Behav Res Ther 2013;51:68–74.
- 44. Wald J, Taylor S. Preliminary research on the efficacy of virtual reality exposure therapy to treat driving phobia. Cyberpsychol Behav 2003;6:459–65.
- 45. Klinger E, Bouchard S, Légeron P, et al. Virtual reality therapy versus cognitive behavior therapy for social phobia: a preliminary controlled study. Cyberpsychol Behav 2005;8:76–88.
- Robillard G, Bouchard S, Dumoulin S, Guitard T, Klinger E. Using virtual humans to alleviate social anxiety: preliminary report from a comparative outcome study. Stud Health Technol Inform 2010;154:57–60.
- 47. Anderson PL, Price M, Edwards SM, et al. Virtual reality exposure therapy for social anxiety disorder: a randomized controlled trial. J Consult Clin Psychol 2013;81:751–60.
- 48. Harris SR, Kemmerling RL, North MM. Brief virtual reality therapy for public speaking anxiety. Cyberpsychol Behav 2002;5:543–50.
- Wallach HS, Safir MP, Bar-Zvi M. Virtual reality cognitive behavior therapy for public speaking anxiety: a randomized clinical trial. Behav Modif 2009;33:314–38.
- 50. Safir MP, Wallach HS, Bar-Zvi M. Virtual reality cognitivebehavior therapy for public speaking anxiety: one-year follow-up. Behav Modif 2012;36:235–46.
- 51. Alsina-Jurnet I, Carvallo-Beciu C, Gutiérrez-Maldonado J. Validity of virtual reality as a method of exposure in the treatment of test anxiety. Behav Res Methods 2007;39:844–51.
- Gutiérrez-Maldonado J, Magallón-Neri E, Rus-Calafell M, Peñaloza-Salazar C. Virtual reality exposure therapy for school phobia. Anu Psicología 2009;40:223–36.
- 53. Gonçalves R, Pedrozo AL, Coutinho ESF, Figueira I, Ventura P. Efficacy of virtual reality exposure therapy in the treatment of PTSD: a systematic review. PLoS One 2012;72:e48469.
- 54. Rothbaum BO, Hodges L, Alarcon R, et al. Virtual reality exposure therapy for PTSD Vietnam veterans: a case study. J Trauma Stress 1999;12:263–71.
- Difede J, Hoffman HG. Virtual reality exposure therapy for World Trade Center post-traumatic stress disorder: a case report. Cyberpsychol Behav 2002;5:529–35.
- 56. Freedman SA, Hoffman HG, Garcia-Palacios A, Weiss PL, Avitzour S, Josman N. Prolonged exposure and virtual reality–enhanced imaginal exposure for PTSD following a terrorist bulldozer attack: a case study. Cyberpsychol Behav Soc Netw 2010;13:95–101.
- 57. Rothbaum BO, Hodges LF, Ready D, Graap K, Alarcon RD. Virtual reality exposure therapy for Vietnam veterans with posttraumatic stress disorder. J Clin Psychiatry 2001;62: 617–22.
- Walshe DG, Lewis EJ, Kim SI, O'Sullivan K, Wiederhold BK. Exploring the use of computer games and virtual reality in exposure therapy for fear of driving following a motor vehicle accident. Cyberpsychol Behav 2003;6:329–34.
- 59. Difede J, Cukor J, Jayasinghe N, et al. Virtual reality exposure therapy for the treatment of posttraumatic stress disorder following September 11, 2001. J Clin Psychiatry 2007;68:1639–47.
- 60. Ready DJ, Gerardi RJ, Backscheider AG, Mascaro N, Rothbaum, BO. Comparing virtual reality exposure therapy to present-centered therapy with 11 US Vietnam veterans with PTSD. Cyberpsychol Behav Soc Netw 2010;13:49–54.
- Reger GM, Holloway KM, Candy C, et al. Effectiveness of virtual reality exposure therapy for active duty soldiers in a military mental health clinic. J Trauma Stress 2011;24:93–6.
- 62. Rizzo A, Difede J, Rothbaum BO, et al. Development and early evaluation of the virtual Iraq/Afghanistan exposure therapy system for combat-related PTSD. Ann N Y Acad Sci 2010; 1208:114–25.

- 63. McLay RN, Wood DP, Webb-Murphy JA, et al. A randomized, controlled trial of virtual reality–graded exposure therapy for post-traumatic stress disorder in active duty service members with combat-related post-traumatic stress disorder. Cyberpsychol Behav Soc Netw 2011;14:223–9.
- 64. Rothbaum BO, Price M, Jovanovic T, et al. A randomized, double-blind evaluation of D-cycloserine or alprazolam combined with virtual reality exposure therapy for posttraumatic stress disorder in Iraq and Afghanistan War veterans. Am J Psychiatry 2014;171:640–8.
- 65. Difede J, Cukor J, Wyka K, et al. D-cycloserine augmentation of exposure therapy for posttraumatic stress disorder: a pilot randomized clinical trial. Neuropsychopharmacology 2014; 39:1052–8.
- 66. Reger GM, Koenen-Woods P, Zetocha K, et al. Randomized controlled trial of prolonged exposure using imaginal exposure vs. virtual reality exposure in active duty soldiers with deployment-related posttraumatic stress disorder (PTSD). J Consult Clin Psychol 2016;84:946–59.
- Botella C, Baños RM, Villa H, Perpiñá C, García-Palacios A. Virtual reality in the treatment of claustrophobic fear: a controlled, multiple-baseline design. Behav Ther 2000;31:583–95.
- 68. Penate W, Pitti CT, Bethencourt JM, de la Fuente J, Gracia R. The effects of a treatment based on the use of virtual reality exposure and cognitive-behavioral therapy applied to patients with agoraphobia. Int J Clin Health Psychol 2008;8:5–22.
- 69. Pitti C, Peñate W, de la Fuente J, et al. [Agoraphobia: combined treatment and virtual reality. Preliminary results]. Actas Esp Psiquiatr 2008;36:94–101.
- Vincelli F, Anolli L, Bouchard S, Wiederhold B, Zurloni V, Riva G. Experiential cognitive therapy in the treatment of panic disorders with agoraphobia: a controlled study. Cyberpsychol Behav 2003;6:321–8.
- 71. Malbos E, Rapee RM, Kavakli M. A controlled study of agoraphobia and the independent effect of virtual reality exposure therapy. Aust N Z J Psychiatry 2013;47:160–8.
- 72. Choi YH, Vincelli F, Riva G, Wiederhold BK, Lee JH, Park KH. Effects of group experiential cognitive therapy for the treatment of panic disorder with agoraphobia. Cyberpsychol Behav 2005;8:387–93.
- 73. Pelissolo A, Zaoui M, Aguayo G, et al. Virtual reality exposure therapy versus cognitive behavior therapy for panic disorder with agoraphobia: a randomized comparison study. J Cyber Ther Rehabil 2012;5:35–43.
- 74. Botella C, García-Palacios A, Villa H, et al. Virtual reality exposure in the treatment of panic disorder and agoraphobia: a controlled study. Clin Psychol Psychother 2007;14:164–75.
- 75. Gorini A, Pallavincini F, Algeri D, Repetto C, Gaggioli A, Riva G. Virtual reality in the treatment of generalized anxiety disorders. Stud Health Technol Inform 2010;8:831–5.
- 76. Belloch A, Cabedo E, Carrió C, Lozano-Quilis JA, Gil-Gómez JA, Gil-Gómez H. Virtual reality exposure for OCD: is it feasible? Rev Psicopatologia Psicologia Clin 2014;19: 37–44.
- 77. Kim K, Kim CH, Cha KR, et al. Anxiety provocation and measurement using virtual reality in patients with obsessivecompulsive disorder. Cyberpsychol Behav 2008;11:637–41.
- 78. Freeman D, Bradley J, Antley A, et al. Virtual reality in the treatment of persecutory delusions: randomised controlled experimental study testing how to reduce delusional conviction. Br J Psychiatry 2016;209:62–7.
- 79. Ku J, Han K, Lee HR, et al. VR-based conversation training program for patients with schizophrenia: a preliminary clinical trial. Cyberpsychol Behav 2007;10:567–74.
- 80. Rus-Calafell M, Gutiérrez-Maldonado J, Ribas-Sabaté J. A virtual reality-integrated program for improving social skills

in patients with schizophrenia: a pilot study. J Behav Ther Exp Psychiatry 2014;45:81–9.

- 81. Park KM, Ku J, Choi SH, et al. A virtual reality application in role-plays of social skills training for schizophrenia: a randomized, controlled trial. Psychiatry Res 2011;189:166–72.
- Hoffman HG, Patterson DR, Carrougher GJ, Sharer SR. Effectiveness of virtual reality–based pain control with multiple treatments. Clin J Pain 2001;17:229–35.
- Gershon J, Zimand E, Lemos R, Rothbaum BO, Hodges L. Use of virtual reality as a distracter for painful procedures in a patient with pediatric cancer: a case study. Cyberpsychol Behav 2003;6:657–60.
- 84. Das DA, Grimmer KA, Sparnon AL, McRae SE, Thomas BH. The efficacy of playing a virtual reality game in modulating pain for children with acute burn injuries: a randomized controlled trial. BMC Pediatr 2005;5:1.
- van Twillert B, Bremer M, Faber AW. Computer-generated virtual reality to control pain and anxiety in pediatric and adult burn patients during wound dressing changes. J Burn Care Res 2007;28: 694–702.
- Hoffman HG, Richards TL, Coda B, et al. Modulation of thermal pain-related brain activity with virtual reality: evidence from fMRI. Neuroreport 2004;15:1245–8.
- Keefe FJ, Huling DA, Coggins MJ, et al. Virtual reality for persistent pain: a new direction for behavioral pain management. Pain 2012;153:2163–6.
- Gromala D, Tong X, Choo C, Karamnejad M, Shaw CD. The virtual meditative walk: virtual reality therapy for chronic pain management. In: Proceedings of the 33rd annual Association for Computing Machinery conference on human factors in computing systems. New York: Association for Computing Machinery, 2015:521–4.
- Garcia-Palacios A, Herrero R, Vizcaíno Y, et al. Integrating virtual reality with activity management for the treatment of fibromyalgia: acceptability and preliminary efficacy. Clin J Pain 2015;31:564–72.
- 90. Sharar SR, Miller W, Teeley A, et al. Applications of virtual reality for pain management in burn-injured patients. Expert Rev Neurother 2008;8:1667–74.
- 91. Kuntze MF, Stoermer R, Mager R, Roessler A, Mueller-Spahn F, Bullinger AH. Immersive virtual environments in cue exposure. Cyberpsychol Behav 2001;4:497–501.
- 92. Saladin ME, Brady KT, Graap K, Rothbaum BO. A preliminary report on the use of virtual reality technology to elicit craving and cue reactivity in cocaine dependent individuals. Addict Behav 2006;31:1881–94.
- Park CB, Park SM, Gwak AR, et al. The effect of repeated exposure to virtual gambling cues on the urge to gamble. Addict Behav 2015;41:61–4.

- Choi JS, Park S, Lee JY, et al. The effect of repeated virtual nicotine cue exposure therapy on the psychophysiological responses: a preliminary study. Psychiatry Invest 2011;8:155–60.
- 95. Thompson-Lake DG, Cooper KN, Mahoney JJ 3rd, et al. Withdrawal symptoms and nicotine dependence severity predict virtual reality craving in cigarette-deprived smokers. Nicotine Tob Res 2015;17:796–802.
- Yoon JH, Newton TF, Haile CN, et al. Effects of D-cycloserine on cue-induced craving and cigarette smoking among concurrent cocaine- and nicotine-dependent volunteers. Addict Behav 2013;38:1518–26.
- Culbertson CS, Shulenberger S, De La Garza R, Newton TF, Brody AL. Virtual reality cue exposure therapy for the treatment of tobacco dependence. J Cyber Ther Rehabil 2012;5: 57–64.
- Riva G, Bacchetta M, Baruffi M, Rinaldi S, Vincelli F, Molinari E. Virtual reality–based experiential cognitive treatment of obesity and binge-eating disorders. Clin Psychol Psychother 2000;7:209–19.
- Riva G, Bacchetta M, Baruffi M, Molinari E. Virtual reality– based multidimensional therapy for the treatment of body image disturbances in obesity: a controlled study. Cyberpsychol Behav 2001;4:511–26.
- 100. Perpiñá C, Botella C, Baños R, Marco H, Alcañiz M, Quero S. Body image and virtual reality in eating disorders: is exposure to virtual reality more effective than the classical body image treatment? Cyberpsychol Behav 2009;2:149–55.
- 101. Marco JH, Perpina C, Botella C. Effectiveness of cognitive behavioral therapy supported by virtual reality in the treatment of body image in eating disorders: one year follow-up. Psychiatry Res 2013;209:619–25.
- 102. Lahiri U, Bekele E, Dohrmann E, Warren Z, Sarkar N. A physiologically informed virtual reality based social communication system for individuals with autism. J Autism Dev Disord 2015;45:919–31.
- Kandalaft MR, Didehbani N, Krawczyk DC, Allen TT, Chapman SB. Virtual reality social cognition for young adults with high-functioning autism. J Autism Dev Disord 2013;43:34–44.
- Mitchell P, Parsons S, Leonard A. Using virtual environments for teaching social understanding to 6 adolescents with autistic spectrum disorders. J Autism Dev Disord 2007;37:589–600.
- McCann RA, Armstrong CM, Skopp NA, et al. Virtual reality exposure therapy for the treatment of anxiety disorders: an evaluation of research quality. J Anxiety Disord 2014;28:625–31.
- Page S, Coxon M. Virtual reality exposure therapy for anxiety disorders: small samples and no controls? Front Psychol 2016;7:326.
- 107. Meyerbröker K, Emmelkamp PM. Virtual reality exposure therapy in anxiety disorders: a systematic review of process-and-outcome studies. Depress Anxiety 2010;27:933–44.