Virtual Reality Applications for the Assessment and Treatment of PTSD

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War is one of the most challenging situations that a human being can encounter. The physical, emotional, cognitive, and psychological demands of a combat environment place tremendous stress on even the most well-prepared military people. It is no surprise that the stressful experiences, characteristics of operations in Iraq and Afghanistan, have produced significant numbers of service members (SMs) and veterans at risk for posttraumatic stress disorder (PTSD), as well as other psychosocial/behavioral health conditions. For example, as of June 2015, the Defense Medical Surveillance System reported 138,197 active duty SMs had been diagnosed with PTSD (Fischer, 2015). In a meta-analysis of studies published since 2001, 13.2% of infantry service members met the criteria for PTSD, with incidence rising dramatically to 25–30% in units with high levels of direct combat exposure (Kok, Herrell, Thomas, & Hoge, 2012). Moreover, as of early 2013, the prevalence of PTSD among discharged veterans receiving treatment at Veteran Affairs (VA) clinics was reported to be 29% (Fischer, 2013). These findings make a compelling case for a continued focus on developing and enhancing the availability of diverse evidence-based treatment options to address this military behavioral healthcare challenge.

One emerging area of research and clinical focus is of the use of Virtual Reality (VR) simulation technology as a tool for delivering evidence-based approaches for the assessment

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and treatment of PTSD. Although in recent times, the popular media has lavishly reported on VR's potential impact on all elements of our evolving digital culture, and has created the impression that VR is a novel technology, the reality is that VR is not a new concept, and many of its developmental roots are traceable to the 1980s and 1990s (Schnipper et al., 2015). Moreover, a large scientific literature has emerged over the last 20 years demonstrating the unique and added value that is accrued with the use of VR to address a wide range of clinical health conditions (Rizzo 1994; Rizzo et al., 1997; 2002; 2010; 2014; Rizzo, Cukor et al., 2015). Within that context, the present chapter will summarize the ways that researchers and clinicians have employed VR to create relevant simulations that can be applied to the assessment and treatment of PTSD.

Virtual Reality: A Revolutionary Tool for Addressing Clinical Health Conditions

During the computer revolution of the 1990s, emerging technologically-driven innovations in behavioral healthcare began to be considered and prototyped (modeled). Early works from this period attempted to use computer technology to enhance productivity in patient documentation and record-keeping, provide cognitive training and rehabilitation, improve access to clinical care via Internet-based teletherapy, and apply VR simulations to deliver exposure therapy for treating specific phobias (Rothbaum, Hodges, & Kooper, 1995). When discussion on the possibility of using VR for human research and clinical intervention first emerged in the early 1990s, the necessary technology needed to deliver on this vision was not available. As a consequence, during these early years VR suffered from an imbalance between what was expected and what could be delivered, as most who explored VR at that time would attest. Computers were slow, 3D graphics were primitive, and head mounted displays (HMDs) were costly, bulky, and had low resolution and limited fields of view.

Over the past 20 years however, VR systems technology has caught up with the original vision. Dramatic advances in the underlying VR-enabling technologies, such as computational speed, 3D graphics rendering, audio/visual/haptic displays, user interfaces and tracking, voice recognition, intelligent agents, and authoring software have supported the creation of low-cost, yet sophisticated, immersive VR systems capable of running on standard level personal computers. Driven in part by the gaming and entertainment sectors, as well as the seeming insatiable global demand for mobile and interactive networked consumer products, advances in technological prowess and accessibility have yielded the software and hardware platforms needed to produce more high fidelity and adaptable VR scenarios for human research and clinical intervention. As VR becomes faster, better, and cheaper moving forward into the twenty-first century, behavioral health applications can now usefully leverage the interactive and immersive assets that VR provides (Rizzo & Koenig, 2017).

Currently, VR can be understood as an advanced form of human–computer interaction (Rizzo et al., 1997) that enables the user to interact with the computers and digital content in a more natural and sophisticated manner compared to what is provided by standard keyboard or pointing devices. Immersive VR can be produced by combining computers, head-mounted displays (HMDs), body-tracking sensors, specialized interface devices, and real-time graphics to immerse a participant in a computer-generated simulated world that changes in a natural or intuitive way with head and body motion. The use of an HMD and head-tracking system affords the delivery of real-time 3D graphic imagery and sounds of a simulated virtual scene, all rendered in relation to user movements and corresponding to what the individual would see and hear if the scene were real. Thus, an engaged virtual experience creates the illusion of being immersed in a virtual space within which users can move and interact.

Some of the clinical areas where VR has been usefully applied would include fear reduction in those with specific phobias (Parsons & Rizzo, 2008; Powers & Emmelkamp, 2008), PTSD treatment (Botella et al., 2015; Difede & Hoffman, 2002; Difede et al., 2007, 2013; Rizzo et al., 2010; Rizzo, Cukor, et al., 2015; Rothbaum et al., 2001, 2014), reducing discomfort in cancer patients undergoing chemotherapy (Schneider, Kisby, & Flint et al., 2010), acute pain reduction for burn patients during wound care and physical therapy (Hoffman et al., 2011) and other painful procedures (Gold, Kim, Kant, Joseph, & Rizzo, 2006), body image disturbances in patients with eating disorders (Riva, 2011), navigation and spatial training for patients with motor impairments (Stanton, Foreman, & Wilson, 1998; Rizzo et al., 2004), and motor rehabilitation and functional skill training in patients with central nervous system dysfunction (e.g., stroke, TBI, SCI, cerebral palsy, multiple sclerosis, etc.) (Holden, 2005; Merians et al., 2002, Lange et al., 2012; Klamroth-Marganska et al., 2014). VR approaches have also proven useful in the assessment and rehabilitation of attention, memory, spatial skills, and other cognitive functions in both clinical and unimpaired populations (Brooks et al., 1999; Brown, Kerr, & Bayon, 1998; Matheis et al., 2007; Parsons, Rizzo, Rogers, and York, 2009; Pugnetti et al., 1995; Rizzo et al., 1994, 2006; Rose, Brooks, & Rizzo, 2005).

In order to meet the needs of these diverse populations, VR scientists have constructed virtual battlefields, social settings, airplanes, skyscrapers, spiders, fantasy worlds, and the more mundane (but still highly relevant) functional environments of the office, home, street, and supermarket. Using VR, clinicians can now create virtual environments that mimic real or imagined worlds, and then apply them clinically to immerse patients in simulations that support the aims and procedures of particular therapeutic or assessment approaches (Rizzo, Parsons, et al., 2011). This has led to a growing consensus that VR has developed into a valuable tool in clinical care (Norcross et al., 2013) and research (Corey, Alicea, & Biocca, 2011).

It was the onset of conflicts in Afghanistan and Iraq and the subsequent need to provide psychological treatment the significant numbers of US service members (SMs) returning from the battlefront with traumatic injuries that really drove an intensive focus on how computer technology could be marshaled to enhance, expand, and extend the reach of clinical care. The urgency of war essentially led to substantial US government funding that served to foster innovations in behavioral healthcare technology to: (1) advance the development and delivery of evidence-based treatments for behavioral health conditions; and (2) reduce "barriers to care" by investigating ways to improve the awareness, anticipated benefit, availability, access, appeal, acceptance, and adherence of/to evidence-based treatments and services (IOM, 2012, 2014). This heightened U.S. Department of Defense (DoD) and the Department of Veteran Affairs (VA) focus and support was most dramatically seen in research efforts to enhance the understanding and treatment of traumatic brain injury, PTSD, and comorbid health conditions. It is within this historical context that the DoD/VA supported R&D using Clinical VR technology to advance the assessment and treatment of PTSD.

Combat-Related PTSD and VR Exposure Therapy

Among the many approaches that have been used to treat persons with PTSD, Prolonged Exposure (PE) therapy (Foa, Hembree, & Rothbaum, 2007) has particular scientific evidence in support of its therapeutic efficacy (IOM, 2012, 2014). PE is a form of individual psychotherapy based on the emotional processing theory of Foa and Kozak (1986). This theory posits phobic disorders and PTSD involve pathological fear structures that are activated when information represented in those structures is encountered, and that this process is at the center of phobic disorders and PTSD (Foa & Kozak, 1986).

According to Foa and Kozak's seminal 1986 paper on emotional processing theory, fear is activated through associative networks that combine information about the activating or feared stimulus, appraisal of its capacity for threat or danger, and previous history of escape/avoidance responses to it. Maladaptive beliefs about the anticipated impact of the feared stimulus, such as, "I can't handle this" or "This will kill me," lead to the creation of fear structures in which essentially harmless stimuli are associated with danger and produce a more generalized appraisal of the world as a dangerous place. This belief then manifests itself in cognitive and behavioral avoidance strategies that prevent confrontation with the feared stimulus and consequently limit the opportunity for exposure to potentially corrective information that could alter the fear structure and result in reduced fear or anxiety. In persons with phobias and PTSD, the chronic avoidance of feared situations leads to an intrinsically rewarding, albeit temporary, sense of relief. Without treatment, these disorders are perpetuated by the anxiety reducing reinforcement derived from the overuse of avoidance as a primary coping strategy. Successful treatment requires emotional processing of the fear structures to modify their pathological associative elements so that objectively harmless stimuli are no longer a cue for the experience of fear/anxiety. Thus, any method capable of activating the fear structure and modifying it in a safe environment would be predicted to improve symptoms of anxiety (Rizzo, Difede, et al., 2013). Possible mechanisms for reducing fear symptoms involve activation and emotional processing, extinction/habituation of the anxiety, cognitive reprocessing of pathogenic meanings, learning new responses to previously feared stimuli, and ultimately integrating corrective and non-pathological information into the fear structure (Foa & Hearst-Ikeda, 1996).

The use of VR to address psychological disorders began in the mid-1990s with its use as a tool to deliver exposure therapy targeting anxiety disorders, primarily for specific phobias (e.g., heights, flying, spiders, enclosed spaces, etc.) (Scozzari & Gamberini, 2011). At the time, VR was seen to be capable of immersing an individual in a digital 3D graphic rendering of a feared environment, within which activation and modification of the fear structure was possible. PE was the first psychological treatment to use VR, in part due to the intuitive match between what the technology could deliver and the theoretical requirement of PE to systematically expose users to progressively more challenging stimuli to activate the fear structure (Rothbaum et al., 1995).

To treat PTSD, PE typically involves the graded and repeated imaginal reliving and narrative recounting of the traumatic event by the patient within the safety of the therapeutic setting. While PE relies mainly on imagination and sensory memory, the exposure process is not simply passive. Patients are asked to verbally recount and describe their trauma experience in the first person with eyes closed, just as if it were happening again and with as much attention as possible to sensory detail. Using clinical judgment, the therapist might prompt the patient with questions about their experience or provide encouraging remarks as deemed necessary to facilitate the recounting of the trauma narrative. This approach [is thought to generate a] low-threat environment where the patient can confront and process trauma-relevant memories and emotions, as well as decondition the learning cycle of the disorder via extinction learning.

A number of studies on a variety of trauma populations have established the efficacy of imaginal PE (Bryant, 2005; Rothbaum & Schwartz, 2002; Van Etten & Taylor, 1998); however, not all patients are able and willing to effectively visualize the traumatic event, and this may result in treatment failure (Yeh et al., 2009). In fact, avoidance of reminders of the trauma is inherent in PTSD and is one of the cardinal symptoms of the disorder. To address this problem, researchers have explored the use of VR as a tool to deliver exposure therapy (VRET). The rationale for this is straightforward. The VR delivery of an evidence-based PE protocol is seen as a way to immerse users in simulated environments that are relevant to the patient's' trauma, where the emotional intensity of the scene is under the precise control of the clinician, and the pace and relevance is customized for each individual.

Through this method, VRET directly delivers multi-sensory and context-relevant cues, which aid in the retrieval, confrontation, and processing of traumatic experiences, in order to circumvent the natural avoidance tendency (Rizzo, Cukor et al., 2015, p. 3). Within a VR environment, the hidden world of the patient's imagination is not exclusively relied upon, in effect taking some of the weight off their shoulders. Previous success in similarly using VRET for persons with other anxiety disorders, such as specific phobias, has been documented in multiple independent meta-analyses and reviews of the literature (Parsons & Rizzo, 2008; Powers & Emmelkamp, 2008; Scozzari & Gamberini, 2011; Opris et al., 2012), most recently in Botella et al. (2015). As well, multiple studies report positive outcomes using VRET with non-OEF/OIF PTSD patients who were unresponsive to a previous course of *imaginal-only* PE treatment (Difede et al., 2007; Rothbaum et al., 2001).

The use of VR as a PE delivery system may also have potential advantages for breaking down barriers to care by increasing treatment appeal, acceptability and adherence by those needing care. Early research on client satisfaction with VRET in a sample of clients with PTSD due to motor vehicle accidents indicated that all participants scored 30 or more on a scale ranging from 8 to 32, indicating high levels of satisfaction with VRET (Beck et al., 2007). In another civilian PTSD sample, Baños et al. (2009) reported increased satisfaction in PTSD clients following a course of VRET, while another group reported equivalent satisfaction between VRET and imaginal exposure (De la Rosa & López, 2012). However, in the later study, while all participants rated both treatments as useful and stated that they would recommend them to a friend or family member who had PTSD, significant differences in the degree of aversion were reported in the VRET group. This finding is similar to findings from a previous study using VRET to treat specific phobias where participants reported that they found it easier to take the first step to confront their fears in a VR environment (García-Palacios, Botella, Hoffman, & Fabregat, 2007). Moreover, the current generation of military SMs and veterans, having grown up with digital gaming technology, may actually be more comfortable with participation in a technology-based VRET approach and this could lead to increased accessing of care. In a survey study to assess this in 325 OIF/OEF active duty Army SMs (Wilson, Onorati, Mishkind, Reger, & Gahm, 2008), results indicated that 83% of the participants reported that they were neutral-to-very-willing to use some technology as part of a treatment; 71% were equally willing or more willing to use a treatment based on technology than to merely talk to a therapist in a traditional treatment. Most interesting is that 20% of SMs who were not willing to seek traditional psychotherapy rated their willingness to use a VR-based treatment as neutral-to-very-willing. One possible interpretation of this finding is that a subgroup of this sample of SMs had a substantial disinterest in traditional mental health treatment, but would be willing to pursue treatment using a VR-based approach. Thus, VRET may offer an appealing treatment option for "digital generation" SMs and veterans who may be reluctant to seek out what they perceive as traditional talk therapies. However, further research on treatment attraction and adherence with military samples is still needed to confirm this conjecture. Finally, VR also provides an objective and consistent format for documenting the sensory stimuli that the patient is exposed to that is not possible when operating exclusively within the unseen world of the patient's imagination.

Development of the Virtual Iraq/ Afghanistan VRET System

In anticipation of impending military behavioral health needs, and supported by a clear theoretical rationale and the extant literature, the USC Institute for Creative Technologies developed an initial prototype Virtual Iraq VRET system in 2004 for conducting user tests to determine feasibility. This was followed by the creation of a full Virtual Iraq/Afghanistan VRET system developed during 2005–2007, funded by the US Office of Naval Research. The system was the product

of both theory-driven design and iterative user-centered feedback cycles with OEF/OIF service members to maximize its ultimate credibility/relevance for clinical users. Preclinical user-testing was conducted at Ft. Lewis, Washington and within an Army Combat Stress Control Team in Iraq (Reger et al., 2009). The testing, which was done on non-diagnosed SMs and clinical users, provided critical input that continues today to improve and evolve the content and usability of the current clinical VRET system.

The 2007 system consisted of four customizable scenarios designed to represent relevant contexts for VRET: three HUMVEE driving scenarios within Iraq, Afghanistan, and USA-themed settings and a 24-block middle-eastern city that was navigable in a dismounted patrol format. General navigation for driving used a standard *Logitech F310* game pad and when interacting in the dismounted foot patrol, an *Ion GoPad* thumb mouse affixed to a user-held mock M4 gun supported foot travel in the virtual simulations. The simulation's real-time 3D scenes were presented using Emergent's *Gamebryo* as the rendering engine, with the visual stimuli presented within an orientation-tracked *Emagin Z-800* head mounted display (HMD). As described by Rizzo et al. (2009):

> Directional 3D audio, vibrotactile and olfactory stimuli of relevance could also be delivered to users. Such stimuli could be controlled and modified in real time by the clinician via a separate "Wizard of Oz"-type clinician interface. This interface is a key feature that allows clinicians to customize the therapy experience to the individual needs of the patient. Using the interface, clinicians can place users in various VR scenario locations that resemble the settings in which the patient's trauma-relevant events had occurred. Ambient lighting and sound conditions can be modified to match the patient's description of their experience and the clinician can then gradually introduce and control real time trigger stimuli (e.g., gunfire, explosions, insurgent attacks, etc.). This level of clinician control is required to foster the anxiety modulation needed for therapeutic extinction and emotional processing in a fashion customized to the patient's past experience and treatment progress (Virtual Reality Exposure). This system was disseminated to over 70 "early-adopter" clinical sites (e.g., VA Medical Centers, military, university and private clinics) for use as a tool to deliver PE and to collect outcome data as to its effectiveness. (Rizzo et al., 2009)

The use of a VR HMD to immerse the user within these controlled stimulus environments is believed to help support user engagement with typically avoided trauma-relevant experiences as required to activate the emotions needed for therapeutic exposure to occur. In fact, research on this aspect of PTSD treatment suggests that the inability to emotionally engage (*in imagination*) is a predictor for negative treatment outcomes (Jaycox, Foa, & Morral, 1998). Thus, VRET offers a way to circumvent the natural avoidance tendency by directly delivering multisensory and context-relevant cues that aid in the confrontation and processing of traumatic memories without demanding that the patient actively try to access his/her experience through effortful memory retrieval. However, future research is needed to compare the relative effectiveness of delivering VR simulation content on a less immersive large-screen display compared to a HMD with PTSD patients to examine the value of immersion on engagement with trauma memories.

VRET Treatment Procedures

The VRET treatment procedure follows the standard evidence-based protocol for "imagination-only" PE therapy (Foa et al., 2007) and consists of weekly, 90–120 min individualized and patient-driven sessions over 10 weeks. During the first session, the clinician generally aims to develop a working therapeutic alliance with the patient as is standard for most clinical approaches. The clinician may attempt to identify and discuss some of the patient's trauma experiences, provide psychoeducation on trauma and PTSD, and present instruction on a deep breathing technique for general stress management purposes. The second session follows up on topics from session 1 as needed and then focuses on providing the patient with a clear explanation and rationale for PE. In some cases, the patient is engaged in light practice with imaginal exposure that focuses on less provocative elements of their trauma experience.

In session 3, the rationale for VRET is introduced and the patient is encouraged to explore a personally relevant area of the *Virtual Iraq/Afghanistan* environment without recounting any trauma narrative for approximately 25 min, with no provocative trigger stimuli introduced. The purpose of this is to allow the participant to learn how to navigate the system, and to function as a "bridge session" from imaginal alone to imaginal exposure combined with VRET. Sessions four through ten are conducted when the VRET proper is conducted with the participant engaging in the VR while verbally recounting the trauma narrative. The goal of this active exposure approach is for the patient to experience a moderate, yet manageable level of anxiety as they are encouraged to activate, confront and process difficult trauma memories and emotions that they have typically avoided (and in some cases never discussed with anyone). When conducted in the safe and supportive clinical setting, at a pace that the patient can handle, anxiety typically reduces over time by way of a learning process referred to as "extinction." As this occurs, the patient is encouraged to further confront more provocative elements in the VR scenarios that the clinician can introduce in real time via the clinician control panel. The treatment also includes homework, such as requesting the participant to listen to an audiotape of their exposure narrative from the most recent session as a form of continual exposure for processing the trauma outside of the treatment setting. Assessment of PTSD status is typically done with a combination of self-report symptom questionnaires, structured interview methods, and sometimes active psychophysiological reactivity tests. A more detailed description of this system, PTSD assessment procedures, and the methodology for a standard VRET clinical protocol can be found elsewhere (Rothbaum et al., 2008).

Research Outcomes

Initial Case Studies and Open Clinical Trials Early clinical tests of the Virtual Iraq/Afghanistan system produced some promising results. Initially, three published case studies reported positive results using this system (Gerardi Rothbaum, Ressler, Heekin, & Rizzo, 2008; Reger & Gahm, 2008; Rizzo et al., 2007). In the first-open clinical trial, analyses of 20 active duty treatment completers also showed positive clinical outcomes (Rizzo et al., 2010). For this sample, mean pre/post PCL-M (Blanchard et al., 1996) scores decreased in a statistical and clinically meaningful fashion (Rizzo, Cukor et al., 2015). Correcting for the PCL-M no-symptom baseline of 17 indicated a greater than 50% decrease in symptoms and 16 of the 20 completers no longer met PCL-M criteria for PTSD at posttreatment. Mean Beck Anxiety Inventory (Beck et al., 1988) scores significantly decreased 33%, and mean PHQ-9 (Kroenke & Spitzer, 2002) depression scores decreased 49%. The average number of sessions for "this sample was just under 11. Positive results from uncontrolled open trials are difficult to generalize from and one must be cautious not to make excessive claims based on these early results" (Rizzo, Buckwalter, et al., 2013). However, using an accepted military-relevant diagnostic screening measure (PCL-M), 80% of the treatment completers in the initial VRET sample showed both statistically and clinically meaningful reductions in PTSD, anxiety and depression symptoms, and anecdotal evidence from patient reports suggested that they saw improvements in their everyday life. These improvements were also maintained at three-month posttreatment follow-up (Rizzo, John, et al., 2013). In another open clinical trial (Reger, Holloway, et al., 2011) with active duty Army SMs ($n = 24$), the results indicated significant pre/postreductions in PCL-M scores and a large treatment effect size (Cohen's $d = 1.17$). After an average of 7 sessions, 45% of those treated no longer screened positive for PTSD and 62% had reliably improved.

Initial Randomized Controlled Trials (RCT) In a small RCT (Roy, Costanzo, Blair, & Rizzo, 2014), active duty SM participants with PTSD ($N = 19$) were randomized to VRET ($n = 9$) or imaginal exposure ($n = 10$) and compared to a control group without PTSD ($n = 18$). At the posttreatment

VRET reduced CAPS (Blake et al., 1995) scores ($P < 0.05$) were recorded, whereas the imaginal PE showed no significant changes. Interestingly, both groups showed significant change ($P < 0.05$) on the PCL-M compared to no significant changes in the control group. In another small preliminary quasi-randomized controlled trial (Mclay et al., 2011), using a comparable VRET simulation of Iraq as the ICT version described above, 7 of 10 participants with PTSD showed a 30% or greater improvement with VR, while only 1 of 9 participants in a "treatment as usual" group showed similar improvement. While the results of these two RCTs are variously limited by small sample sizes, lack of blinding, use of a single therapist, and in the case of Mclay et al. (2011), the VRET comparison was with a set of relatively uncontrolled usual care conditions, these findings add to the incremental evidence in support of the use of VRET for combat-related PTSD. The overall trend of these positive findings (in the absence of any reports of negative findings) is encouraging for the view that VRET can be safely applied clinically and may be an effective approach for delivering an evidence-based treatment (PE) for PTSD. At the least, the main conclusion of these studies is that VRET is as efficacious as traditional PE and sometimes may outperform it. However, more research is needed in the form of high quality RCTs before this can be determined with certainty.

Ongoing Randomized Controlled Trials There are currently several clinical trials ongoing to assess the efficacy of the Virtual Iraq/Afghanistan system with SMs and veteran populations. As described by Rizzo, Cuckor et al. (2015):

> One RCT is focusing on comparisons of treatment efficacy between VRE and imaginal PE (Reger & Gahm, 2011) and another is testing VRE compared with VRE + a supplemental care approach, Trauma Management Therapy (Beidel, Frueh, & Uhde, 2010). Another RCT is investigating the additive value of supplementing VRET and PE with a cognitive enhancer called D-cycloserine (DCS) (Difede, Rothbaum, & Rizzo, 2010). DCS, an N-methyl-d-aspartate partial agonist, has been shown to facilitate extinction learning in laboratory animals when infused bilaterally within the amygdala ("fight or flight" conditioning center in the brain) prior to extinction training. Recent evidence of both VRET and DCS effectiveness has been reported by Difede et al. (2013) in a clinical trial with WTC [World Trade Center] PTSD clients. In a double-blinded controlled comparison between VRE+DCS and VRE+Placebo, both groups had clinically meaningful and statistically significant positive outcomes with the DCS group achieving equivalent gains with fewer sessions. (Rizzo, Cuckor et al., 2015)

This finding is in contrast with two reports that found no additive value when adding DCS to imaginal PE for PTSD treatment in civilian (de Kleine, Hendriks, Kusters, Broekman, & van Minnen, 2012) and military (Litz et al., 2012) groups.

Finally, a recent study with 156 OIF/OIF veterans with PTSD compared the effects of DCS, alprazolam, and placebo when added to 5 VRET sessions (Rothbaum et al., 2014). PTSD symptoms significantly improved across all conditions at posttreatment and at the 3-, 6-, and 12-month follow-ups but there were no differences in treatment outcome across medication conditions with the exception of posttreatment and 3-month follow-up CAPS scores indicating that the alprazolam group showed a higher rate of PTSD than the placebo group. The current ongoing RCT (Difede et al., 2010) will be important for determining whether DCS will differentially improve PTSD treatment outcomes across PE and VRET conditions in view of previously reported mixed findings in this literature.

Project BRAVEMIND: Next-Generation Virtual Iraq/Afghanistan VRET System

Based on these encouraging clinical outcomes using VRET to treat combat-related PTSD and the urgency of the need to provide the best care for the expanding numbers of SMs and veterans reporting PTSD symptoms, the US Army funded the development of an updated and expanded version of Virtual Iraq/Afghanistan system in 2011. Now described as *BRAVEMIND*, a primary goal of this effort was to increase the diversity of the VR scenarios and improve the customizability of stimulus delivery to better address the needs of clinical users who have had a diverse range of trauma experiences. This effort was supported by drawing on the vast amount of user feedback generated from both patients' and clinicians' feed-

back from use of the previous 2007 Virtual Iraq/Afghanistan system (Rizzo, Cukor et al., 2015).

The system was rebuilt from the ground up using the state-of-the-art *Unity Game Engine*. The system went from four environments to fourteen. The original four were revamped, and ten new scenarios were added. The new scenarios include a Bagram Air Force Base setting, an industrial zone, a mountainous forward operating base, a roadway checkpoint, a rural Afghan village, separate Iraq and Afghanistan cities, and slum and high-end residential areas. Additional features include customizable sound trigger profiles, expanded weather and time of day controls, selectable Humvee/MRAP/Helicopter vehicles, vehicle-to-foot patrol transitioning, and an updated clinical interface designed with clinician feedback to enhance usability (Rizzo, Cukor et al., 2015).

The *Unity Game Engine* and higher fidelity graphic art/animation have been used to enhance the realism and credibility of the stimulus content while presenting an experience that is uniquely designed to differentiate it from a commercial videogame. The system was also designed to use off-the-shelf components (e.g., standard laptop/PC, head-mounted display, tracking/interface technology, etc.) with the aim to reduce equipment costs to well under $5000. The BRAVEMIND system is now being distributed to clinical sites and has been designed to provide a flexible software architecture that will support the efficient addition of new content for the expansion and diversification of the system as new clinical needs are specified. The research outcomes cited above did not use the new BRAVEMIND system, but the ongoing Difede et al. (2010) and Biedel et al. (2010), RCTs have adopted it and outcomes from these trials are forthcoming. More information on the BRAVEMIND system components is available in a detailed equipment/software manual available from the first author.

BRAVEMIND Expansion for Combat Medics and Victims of Military Sexual Trauma

The 2011 rebuild of the BRAVEMIND system provided an updated software architecture to support the flexible and efficient expansion of the system's content and functionality to support new customizable and relevant options for conducting VRET with a wider range of relevant trauma experiences. The BRAVEMIND VRET system is now being further evolved to address the unique therapeutic needs of combat medics/corpsmen and of persons who have experienced military sexual trauma (MST) with PTSD.

Combat Medics/Corpsman VRET Project Observations from our existing clinical work and from recent reports indicate that there is a growing need to address PTSD in combat medics and corpsman. The primary role of the combat medic (Army and Air Force) and corpsmen (Navy and Marines) is to provide medical treatment to the wounded in a combat environment. Combat medics/corpsmen are a unique population within the ranks of deployed SMs. They serve double duty, both professionally and psychologically. In addition to bearing all the responsibilities of soldiering, medics must calmly treat the devastating wounds of modern warfare and are more exposed than other soldiers to seriously wounded or dead service members. Unlike civilian hospital doctors or nurses, who rarely know their patients, medics have the added pressure of being close to the soldiers they are trying to keep alive. And when one dies, medics often face self-doubt – an emotion they must hide or risk losing the platoon's confidence. Treatment for this population requires specialized VR content that is more relevant to their experiences with emotionally challenging situations that are different from what has been effective with other SMs. Thus, with funding from the Infinite Hero Foundation, the existing BRAVEMIND scenarios were extended to include more wounded virtual humans that can display a range of wounds/burns and manifest realistic injury behaviors. Helicopter insertion and extraction scenarios and a Bagram Air Force Base hospital setting for medic/corpsmen "first receivers" were developed. This effort required the creation of significant new graphic art, motion capture animation, airborne vehicle integration, and a library of digital character content that emulates the injuries common to the combat environment in order to offer relevant VRET for

combat medics/corpsmen with PTSD. These elements are included as part of the currently available system, but no outcome data has been reported thus far on its specific use.

Military Sexual Trauma VRET System PTSD can result from exposure to actual or threatened death, serious injury, or sexual violation. This is of particular relevance for SMs who may face trauma from both the threat that is naturally inherent in the combat theatre, as well as from the possible additive occurrence of sexual violations from within the ranks. Thus, MST that is experienced as a threat or result of an occurrence of a sexual violation/assault within a military context can produce additional risk for the development of PTSD in a population that is already at high risk due to the existing occupational hazards present in the combat environment (see also Thomsen et al., Chap. 21, this volume).

A report issued by the Joint Chiefs, together with the DoD Sexual Assault Prevention and Response Program (SAPR) (DoD, 2012), specifies the need for improvements in advocacy coordination, medical services, legal support, and (behavioral health) counseling for the victim (p. 13). This has become an issue of grave concern within the military, as reports of sexual violations and assaults have not only been on the rise over the last 10 years, but have also garnered significant popular media attention. Overall, 6.1% of women and 1.2% of men (active duty SMs) indicated they experienced unwanted sexual contact in 2012. For women, this rate is statistically significantly higher in 2012 than in 2010 (6.1% vs. 4.4%) (DoD, 2012). A bleaker picture of the problem emerges when reports from postdischarge Veteran surveys are considered. In a nationwide randomly selected sample of women seeking care through VA medical centers, approximately one out of four reported experiencing a sexual trauma while on active duty (Skinner et al., 2000). The reported prevalence rates of MST in women were 20–25% for sexual assault and 24–60% for sexual harassment. Thus, while the DoD is mobilizing to reduce the incidence of MST with novel education and prevention programs, significant effort is also required to develop and disseminate effective treatments to address the existing problem of PTSD due to MST.

The current MST VRET project has developed content for inclusion in the BRAVEMIND architecture that provides new customizable options for conducting VRET with persons who have experienced MST. The novel component in this project involved the creation of new content that was embedded within the existing BRAVEMIND scenarios such as barracks, tents, other living and work quarters, latrines, and other contexts that have been reported by MST victims as in-theatre locations where their sexual assault occurred. Additionally, US military base and civilian contexts were created including barracks, offices, a small town bar area, abandoned lots, motel rooms, and civilian automobile settings. The system does *not* attempt to recreate a sexual assault, but rather, sets up the contexts surrounding the assault in which users can be supported in the therapeutic confrontation and processing of MST memories in accordance with the protocol that has been used previously which implements PE within the simulations (Rothbaum et al., 2008). The new MST content was completed in the summer of 2015 and a pilot RCT is ongoing with a target sample size of 34 male and female participants at Emory University. This has not been attempted previously with immersive VRET, although a nonimmersive VR system in Europe produced initial positive findings with civilian patients having PTSD due to physical assaults and domestic violence (Baños et al., 2011). While both men and women can experience MST, the urgent need for this work is underscored by the growing role of women transitioning into full combat roles in the combat theatre, an area that up to now has been primarily the domain of men.

BRAVEMIND Expansion for the Assessment of PTSD

While VR has been primarily used as a therapeutic tool that aims to enhance the delivery of PE for PTSD, other researchers have begun to explore the reuse of the BRAVEMIND simulation content as stimuli for creating more objective PTS

assessment measures. One of the primary challenges for arriving at an accurate diagnosis of PTSD is that the assessment information is typically limited by reliance upon the patient's subjective reports of his/her traumatic experiences derived from self-report symptom checklists or from structured clinical interview reporting. Many factors can influence the accuracy of this assessment data. Some individuals may under report symptoms because of the stigma of having a mental health disorder, and others may over report symptoms to obtain medical benefits (Gates et al. 2012). Previous research suggests that individuals with PTSD may show differential physiological reactivity in response to specific, emotionally evocative cues and Webb, Vincent, Jin, and Pollack (2015) provide a concise detailing of this literature. Thus, some researchers have attempted to enhance the objective assessment of PTS by combining the capacity of VR to produce highly controlled, ecologically relevant, and realistic stimulus environments that has integrated psychophysiological/biological response measurement. The use of VR stimuli for this purpose is at an early stage of maturity, but encouraging results have been reported in three studies that directly address the VR/PTSD assessment question (Costanzo et al., 2014; Highland et al., 2015; Webb et al., 2015). In a somewhat related effort, another paper has examined the use of fMRI to assess changes in brain activation following a course of VRET and PE (Roy et al., 2014). This falls in line with a view held by some neuroscientists (Corey et al. 2011; Tarr & Warren, 2002) that highly controllable VR-generated content may add value as stimuli in brain imaging studies.

The detection of subthreshold PTSD using BRAVEMIND-derived content was first investigated by Costanzo et al. (2014). While a minority of trauma-exposed individuals is diagnosed with PTSD, a significant number may experience persistent subthreshold symptoms that cause significant impairment and distress (Cukor, Wyka, Jayasinghe, & Difede, 2010). For example, subthreshold PTSD has been associated with increased aggression (Jakupcak et al., 2007), alcohol use (Adams, Boscarino, & Galea, 2006), healthcare utilization, and work absences (Breslau, Lucia, & Davis, 2004). Costanzo et al. (2014) tested a cohort of 78 SMs who had recently returned from deployment to Iraq or Afghanistan, using three two-minute fixed video sequences, which were taken from the original Virtual Iraq/Afghanistan system, as standard stimuli. The video content was viewed by participants on a flatscreen computer monitor. One sequence provided the first-person perspective of someone walking through a middle-eastern marketplace, while the other two provided perspectives from a HUMVEE in a convoy, one as the driver, and the other as the passenger. In each environment, participants were presented with a variety of explosions and other threatening stimuli that became more provocative over the course of the two-minute sequences. During the exposures, heart rate, blood pressure, respiratory rate, skin conductance and electromyographic eye blink response was monitored. Among the range of psychophysiological measures that were studied, regression analysis revealed that heart rate (HR) was most strongly linked with PCL-M-measured PTSD symptom severity, and that HR response across the three VR sequences explained 14% of the variance in the PCL-M scores. As well, HR was most strongly associated with Clinician-Administered PTSD Scale-based measures of hyperarousal ($R2 = 0.11$, $p = 0.035$), re-experiencing ($R2 = 0.24$, $p = 0.001$), and global PTSD symptoms ($R2 = 0.17$, $p = 0.003$). These findings provide initial support for the use of VR-developed stimulus content for eliciting psychophysiological responses associated with subthreshold PTSD symptoms. Such an approach to create more objective measures of symptom severity could help to risk stratify SMs after deployment, and perhaps lead to earlier recommendations to seek treatment, or targeted intervention efforts.

In a similar study, Webb et al. (2015) recorded physiological activity from 58 male veterans with and without PTSD and combat trauma exposure (PTSD Diagnosis $n = 16$; Trauma Exposed/No PTSD Diagnosis: $n = 23$; No Trauma/No PTSD Diagnosis: $n = 19$) in response to emotionally evocative VR stimuli derived from the Virtual Iraq/Afghanistan simulation. Two combat-related videos (i.e., HUMVEE driving scene

and a foot patrol in a Middle Eastern city setting) were presented to users in a VR HMD where stimuli of increasing severity were presented. Within the simulation videos, five stimuli were presented including: an aircraft flying overhead, a mortar explosion, an improvised explosive device (IED), an attack resulting in an explosion, and an attack by an insurgent. The five events occurred at approximately 30, 75, 120, 165, and 210 seconds after the start of the video. Significant differences between the Control, Trauma, and PTSD groups were found for measures of skin conductance and HR interbeat interval features collected during presentation of each of the ten video events (five events of increasing severity per video). These features were entered into three stepwise discriminant function analyses to assess accuracy of classification for Control versus Trauma, Control versus PTSD, and Trauma versus PTSD pairings of participant groups. Leave-one-out cross-validation classification accuracy ranged from 71% to 94% (Webb, et al., 2015). These results further suggest the utility of VR stimuli integrated with objective physiological measures in PTSD assessment. Catecholamine responses as a potential objective biomarker for PTSD have also been studied in SMs who had recently redeployed home (Highland et al., 2015) using the same computer monitor-delivered Virtual Iraq/Afghanistan videos as reported in Costanzo et al. (2014).

While adaptive for acute stress, chronic stress and associated repetitive catecholamine-system activation can lead to damaging biopsychosocial outcomes (Mead, Beauchaine, & Shannon, 2010; Highland et al., 2015). One study using a community sample found that individuals with PTSD had higher 24-hour levels of catecholamines as compared to those without trauma exposure, as well as those exposed to trauma but who did not develop PTSD (Young & Breslau, 2004). Interestingly, those with trauma exposure who did not develop PTSD showed lower catecholamine levels than those without trauma exposure (Young & Breslau, 2004), suggesting a potential mechanism for resilience. Although catecholamine levels are related to PTSD symptomatology, research with postdeployment SMs on catecholamine responses to acute combat-related cues is currently quite limited (Highland et al., 2015).

In Highland et al. (2015), 87 clinically healthy SMs, within 2 months of return from deployment to either Iraq or Afghanistan first completed relevant self-report questionnaires, then viewed the VR combat sequences and completed baseline and post-VR blood draws for catecholamines. A series of simple and multiple linear regressions were used to assess the relations between PCL-M symptom clusters and catecholamine responses with functional status subscales. Overall, the results indicated that norepinephrine (NE) was a far more salient measure than either dopamine or epinephrine. "[NE] responses to the VR combat sequences significantly moderated the relationship between avoidance and functional status subscales, to include physical role functioning ($\beta = .36$, $p = .002$, $q = .02$), vitality ($\beta = .36$, $p = .002$, $q = .02$), and physical functioning ($\beta = .53$, $p < .001$, $q = .001$). For individuals lower in avoidance symptoms, increased NE responses were associated with higher functional status subscale scores. On the other hand, for participants with higher avoidance symptoms, increased NE responses were linked with decreased functional status subscale scores" (Highland et al., 2015). These findings corroborate the evidence found with the psycho-physiologic measures, namely that VR may be used to elicit objective measures of symptom severity and functional status after traumatic experiences. Moreover, these and possibly other genetic and epigenetic biomarkers might hold promise to be incorporated into a model that can effectively risk stratify those who have been exposed to trauma, to facilitate targeted early interventions for those at high risk.

Finally, a small RCT was conducted comparing VRET and PE (see Roy et al., 2014, described above) that also included functional magnetic resonance imaging (fMRI) before and after treatment in a subsample of ten of the study participants (6 PE and 4 VRET). This pilot work aimed to investigate brain activation levels in areas that have been implicated as relevant to the occurrence of PTSD (e.g., hyperactivity in the amygdala, subcallosal gyrus, and the lateral prefrontal cortex, with inhibition in the anterior cingulate

gyrus) (Shin et al., 2005). The subsample consisted of those in the RCT who were not excluded from fMRI scanning procedures due to embedded shrapnel or other contraindications. Stimuli presented in the fMRI system consisted of an Affective Stroop paradigm (Blair et al., 2007) that incorporated neutral, negative, and positive affect photographs from the International Affective Picture System (IAPS) (Lang, Bradley, & Cuthbert, 2008).

For the small subset of participants receiving either form of treatment who also completed fMRI pre and posttreatment, the decrease in mean CAPS scores did not achieve significance, 84.1 (12.62) baseline to 80.67 (14.97), p = 0.12, but for mean PCL scores it did, 64.2 (12.74) to 51.7 (15.49), $p < 0.05$ (c.f. Roy et al., 2014). For this subset of participants at pretreatment baseline, the viewing of emotionally charged IAPS pictures was associated with hyperactivity in the amygdala, subcallosal gyrus, and the lateral prefrontal cortex, along with inhibition in the anterior cingulate gyrus, as had been previously reported (Shin et al., 2005). At the completion of treatment, statistically significant and marked improvement, or normalization, in three brain regions was detected in response to the picture stimuli. Significant reductions in amygdala and increases in ventromedial prefrontal cortex activation levels were detected with negatively charged, but not neutral imagery following treatment. The anterior cingulate cortex also displayed significantly reduced inhibition (improvement) in association with negative, but not neutral, imagery. This was in sharp contrast to a non-PTSD postdeployment control group (n = 18) that showed no significant changes in any of the brain regions during the same repeat scan timeframe. The comparison with the control group supports the view that the changes observed in the treated group were in fact due to the intervening therapy, as opposed to just practice, or comfort with the fMRI procedures and the display of the emotionally charged pictures with repeated viewing. Although the small pre/post scanned subsample precludes a comparison between VRET and PE, the results indicate that fMRI-captured brain activation levels may provide objective evidence both for the presence of PTSD, and the impact of treatment. Future efforts with fMRI assessment of PTSD-related brain activation should examine responses to VR-derived content that resemble core audiovisual elements of the patients' traumatic contexts as has been done with the psychophysiological and catecholamine VR assessment studies. While still in its infancy, more research in this area may produce assessment methods that more objectively assess the presence and ongoing status of PTSD in a fashion that augments what is attainable with self-report.

Future Directions

Clinical interest in the use of VR technology to deliver PE therapy for PTSD and related efforts to use VR content to develop more objective assessment systems has grown as positive outcomes have been reported with their initial implementation. This interest will also likely be fueled by a societal zeitgeist in which this form of immersive and interactive technology has caught the public's attention and imagination. While previously hamstrung by costs, complexity and clinician unfamiliarity with the equipment needed to use VR clinically, VR technology is charging forward in the consumer marketplace with new low-cost, hi-fidelity, and usable product offerings that will likely drive wide scale adoption. This will result in a scenario where "…it is probable that in the next few years, a VR device will be like a toaster – although you may not use it every day, every household will have one. This emerging level of market penetration will likely support accelerated uptake in the healthcare domain as the general public has more virtual experiences and comes to see the potential value of the experiences that VR can create, beyond the world of digital games" (Good, 2016).

In fact, a recent Goldman Sachs market forecast predicted an 80 billion dollar VR market by 2025, with healthcare coming on 2nd place, only behind gaming entertainment (Verhage, 2016). And there is evidence that many clinicians have come to recognize its potential for creating tools that can amplify and extend their capacity to

deliver evidence-based care. This can be seen clearly in the results from a survey in which expert clinicians were queried as to what interventions they predicted would increase in the next decade (Norcross, 2013). VR ranked 4th out of 45 options with other computer-supported methods occupying 4 out of the top 5 rankings.

But the potential interest and growth in the clinical use of VR will not be solely based on popular media excitement and consumer uptake. The use of VR clinically fits well with the conceptualization of psychology as a scientific discipline. The affordances that VR technology provides are ideal for creating controlled stimulus environments. Stimuli can be systematically delivered to users within realistic and relevant simulations of real-world contexts that support exquisite timing and control of stimulus load/complexity, all of which can be manipulated in a dynamic fashion contingent on the needs and responses of the client or research participant. Moreover, within such VR simulations, human performance can be digitally captured in real time in support of a precise and detailed analysis of relevant responses in relation to systematic stimulus presentations. In this regard, VR can be seen as capable of producing the "ultimate Skinner Box" for conducting human research, assessment, and intervention. This is especially relevant for exposure-based treatments that could benefit from the delivery of consistent, controllable, and immersive trauma-relevant stimulus environments that do not rely narrowly on the variable and ultimately hidden world of a patient's imagination. VR also provides an objective and consistent format for documenting the sensory stimuli that the client is exposed to, and one that can be linked precisely to physiological, biological, behavioral, and self-reported reactions for assessment and treatment documentation/research (Rizzo, Cukor et al., 2015).

In addition to these functional stimulus/response quantification assets, the use of VR as a PE delivery system may also be found to break down barriers to care by improving treatment appeal, acceptability, and adherence by those in need of care. The current generation of young military SMs and veterans, many having grown up with digital gaming technology, may be more attracted to and comfortable with participation in a VR therapy approach (Wilson et al., 2008) and this could lead to increased access of care by those in need. While there is evidence in support of this with VR exposure applications with civilians (Baños et al., 2009; Beck et al., 2007; De la Rosa & López, 2012; García-Palacios et al., 2007), more research is needed to determine if VRET is perceived with less stigma by "digital generation" SMs and veterans relative to what they perceive as traditional talk therapies, and will that ultimately serve to increase the accessing of care (Rizzo, Cukor et al., 2015).

While it is intuitively appealing to assume that VRET will likely be an effective treatment for PTSD since it provides a novel and engaging mechanism for delivering an already endorsed, evidence-based approach (Cognitive Behavioral Therapy with exposure), more research is needed to provide stronger scientific support for that claim. The current state of the literature is promising, particularly in view of the strong evidence for VRET effectiveness for delivering exposure treatment for specific phobias. However, the existing research examining VRET for combat-related PTSD provides only preliminary evidence for its efficacy. Positive results from three published case reports, two open trials, two waitlist controlled studies, and two small RCTs have formed the initial basis for support. Results from currently ongoing high-quality RCTs with larger sample-sizes are anticipated to help inform this issue in the near future. As well, while recent VR PTSD assessment studies have reported encouraging findings that could advance the creation of more objective assessment methodologies, more validation studies with larger samples are needed.

Another important direction to pursue in the future will involve the conduct of dismantling studies to better specify what elements of VRET are crucial for differentiating VRET from standard CBT exposure approaches. Such research could lead to improved treatment outcomes by providing a better understanding of the mechanisms that may predict who this treatment may appeal to and who may achieve better clinical outcomes from it. Subject variables including gender, age, video game experience, number of

deployments, and pasttrauma history may provide useful covariates to inform predictions as to who is most suited to benefit from these forms of trauma-focused exposure (VR vs. Imaginal). More research is also needed to study how variations from the standard protocol delivery of VRET in terms of the frequency and duration of sessions, the additive value of multisensory stimuli – i.e., olfaction, and the addition of pharmacological agents (D-cycloserine) or central nervous system-focused procedures (vagal nerve stimulation) – could also impact treatment outcomes within the controlled stimulus environment that is available with a VR simulation. Such Clinical VR research efforts are now more feasible in view of the rapid technological advances that have driven the recent availability of off-the-shelf VR equipment that is cheaper, less complex, and of higher quality than what was available just 2 years ago. Thus, it is likely that the use of VR will continue to drive novel PTSD research and address the significant clinical and social welfare challenges that exist with those who suffer from the experience of trauma.

Finally, the broader general awareness and use of VR for combat-related PTSD assessment and treatment could potentially influence adoption within the civilian sector. If one reviews the history of the impact of war on advances in civilian clinical care, a case can be made that clinical VR will follow this trend and be more widely used as a result of its successful application in the military context. For example, the Army Alpha/Beta Classification Test emerged during World War I because of the demand for better cognitive ability assessment later set the stage for the civilian psychometric testing movement during the postwar era (Rizzo et al., 2011). Later on, the birth of clinical psychology as a treatment-oriented profession was borne from the need to provide care to the many veterans returning from World War II with "battle fatigue" providing the impetus for the VA to create a clinical psychology intern program in the late 1940s. At the same time, the creation of the National Institute of Mental Health (NIMH) came from an executive order from President Harry Truman as a vehicle for addressing the challenge of "combat neurosis." More recently, the Vietnam War led to the recognition and a deeper understanding of PTSD as a definable clinical disorder. Perhaps one of the clinical "game changing" outcomes of the OIF/OEF conflicts could follow from the military's support for research and development into clinical treatment systems that leverage new interactive and immersive technologies such as VR. In turn, this may drive wider uptake of Clinical VR in the civilian sector as the technology becomes more common in the digital landscape of modern society.[1] If past history can predict the future, such advances in health care innovations, driven by the urgency of war, will have a lasting impact on military and civilian mental health care long after the last shot is fired.

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[1] For an extensive collection of videos on this project (simulation videos, patient interviews, media reports), the reader is directed to: https://www.youtube.com/channel/UCQrbzaW3x9wWoZPl4-l4GSA

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