

Enhanced exposure therapy for combat-related Posttraumatic Stress Disorder (PTSD): Study protocol for a randomized controlled trial

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ABSTRACT

Background: PTSD, which has been identified in up to 23% of post-9-11 veterans, often results in a chronic, pernicious course. Thus, effective treatments are imperative. The Institute of Medicine (IOM) concluded that the only intervention for PTSD with sufficient evidence to conclude efficacy is exposure therapy. This Phase III trial compares the efficacy of exposure therapy for combat-related PTSD delivered in two different formats- via virtual reality exposure therapy (VRE) or prolonged exposure therapy (PE)- combined with D-Cycloserine (DCS), a cognitive enhancer shown to facilitate the extinction of fear.

Methods/design: Military personnel of any duty status and civilians deployed to Iraq and Afghanistan were eligible. Participants were randomly assigned to 9 sessions of exposure therapy (VRE or PE) and medication (50 mg DCS or placebo). Participants were treated at three geographically diverse sites. Participants were re-assessed at 3-months post-treatment. The co-primary hypotheses are that (1) DCS will augment response to exposure therapy (both VRE and PE) on PTSD symptoms; (2) VRE will be associated with greater improvement than PE. Genetic and psychophysiological markers will be evaluated as potential moderators and mediators of treatment outcomes as well as secondary outcomes.

Discussion: This study is the first to compare the relative efficacy of DCS-augmented VRE versus PE on PTSD symptoms. The design has several advantages: participants received an active, effective treatment and predictors of response to treatment included genetic and psychobiological measures. The results may directly influence the future delivery of services, and contribute to the development of a standardized treatment protocol.

Trial registration: [NCT01352637](https://clinicaltrials.gov/ct2/show/study/NCT01352637).

Abbreviations: PTSD, Posttraumatic Stress Disorder; IOM, Institute of Medicine; VRE, Virtual Reality Exposure Therapy; PE, Prolonged Exposure Therapy; DCS, D-Cycloserine; US, United States; VR, Virtual Reality; BDNF, Brain Derived Neutrophin Factor; BLA, Basolateral Amygdala; FPS, Fear-potentiated Startle; SCR, Skin Conductance Response; PLA, Placebo; CAPS, Clinician Administered PTSD Scale; SNP, Single Nucleotide Polymorphism; WCMC, Weill Cornell Medical College; NICoE, National Intrepid Center of Excellence; WRNMMC, Walter Reed National Military Medical Center; LBVA, Veterans Administration Long Beach Healthcare System; VA, Veteran's Administration; USAMRMC, U.S. Army Medical Research and Materiel Command; OIF, Operation Iraqi Freedom; OEF, Operation Enduring Freedom; PSS, PTSD Symptom Scale; PCL, Posttraumatic Stress Disorder Checklist; MDD, Major Depressive Disorder; MINI, Mini International Neuropsychiatric Interview; BDI, Beck Depression Inventory; DRR, Deployment Risk and Resilience Inventory; DVVIC, Defense and Veterans Brain Injury Center; THQ, Trauma History Questionnaire; CTQ, Childhood Trauma Questionnaire; BSI-11, Barratt Impulsivity Scale; QOLI, Quality of Life Inventory; CEQ, Client Expectancy Questionnaire; EMG, Electromyography; SCL, Skin Conductance Level; ECG, Electrocardiogram; US, Unconditioned Stimulus; CS, Conditioned Stimulus; NA, Noise Alone; ITIs, Inter-trial Intervals; CSQ, Client Satisfaction Questionnaire; SUDS, Subjective Units of Distress; HMD, Head Mounted Display; ES, Effect Sizes; AR1, First-order Autoregressive; RCT, Randomized Controlled Trial; ICC, Intraclass Correlation Coefficient; SD, Standard Deviation; DSMB, Data Safety Monitoring Board; SSRI, Selective Serotonin Reuptake Inhibitor

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1. Introduction

Posttraumatic stress disorder (PTSD) is a severe, debilitating disorder that is prevalent and difficult to treat among returning United States (U.S.) military personnel [1–3]. Estimates of combat exposure among veterans of the global war on terror range from 5 to 25% [1,4].

The Institute of Medicine (IOM) review of treatments for PTSD concluded that the only intervention with enough evidence to conclude efficacy is exposure therapy [5,6]. Efficacy has been demonstrated in several randomized clinical trials of active duty military personnel and veterans [2,7–13]. However, avoidance of reminders of the trauma is inherent in PTSD. Hence, most people with PTSD never seek treatment [14] and many are unable to effectively engage their emotions. Such patients typically fail to improve, as failure to engage emotionally predicts poor treatment outcome [15]. Virtual Reality (VR) offers a way to confront this avoidance by directly delivering multiple sensory cues that may evoke the trauma without demanding that the patient actively do so. VR treatments may offer a viable method to address barriers to effective treatment, such as finding means to motivate patients and facilitate their emotional engagement in therapy [16].

Reviews estimate that between 30% and 60% of patients do not complete a full course of any type of psychotherapy [17,18]. Agents that maximize treatment benefit are desirable because they are less costly and achieve effects before patients are likely to terminate treatment. Pharmacological agents such as D-cycloserine (DCS) could reduce the number of required exposure sessions by providing faster symptom relief which would make treatment more cost effective and possibly increase the willingness of patients and clinicians to utilize the treatment.

Currently no biomarkers exist to predict treatment response for PTSD. We will test brain derived neurotrophic factor (BDNF) Val66Met genotype as a biomarker predicting treatment response. Research using a novel mouse model of the variant BDNF (Val66Met) that uniquely recapitulates certain endophenotypes of PTSD have shown that Val66Met mice exhibited impaired fear extinction [19]. This learning process depends upon inhibitory projections from the prefrontal cortex to the basolateral amygdala (BLA) to suppress amygdala activation, and is analogous to exposure therapy in humans. Additional single candidate genes will be considered as evidence becomes available suggesting their possible role in PTSD treatment response.

Psychophysiological responses to standardized tasks may be useful predictors of treatment response [20–23]. Fear conditioning methods provide good laboratory tools for testing exaggerated fear and impaired inhibition in PTSD [24]. Early studies with veterans found enhanced fear conditioning in PTSD [25–27]. The acoustic startle response provides an ideal translational tool to investigate fear conditioning, since the amygdala is directly connected with the startle circuit [25,28]. Fear conditioning measures can also provide objective indices of treatment outcome. Studies using fear-potentiated startle (FPS) and skin conductance response (SCR) have found fear extinction deficits in subjects with PTSD [29–31]. PTSD subjects with higher current symptoms show impaired inhibition of fear in the presence of safety cues [32] and during fear extinction [31]. A recent study found that fear inhibition improved after PTSD treatment [33].

2. Materials and methods

2.1. Study aims

The primary aims of this study are 1) to examine the effects of DCS versus placebo (PLA) augmentation of exposure therapy on PTSD symptoms and 2) to examine the relative efficacy of virtual reality enhanced exposure therapy (VRE) and prolonged exposure therapy (PE) on PTSD symptoms. The secondary aims are 1) to examine the interaction of DCS and mode of exposure therapy on PTSD symptoms, 2) to examine genetic markers as moderators of treatment response and 3) to

examine changes in fear conditioning and extinction and treatment response. The co-primary hypotheses are 1) DCS will augment response to exposure therapy (VRE and PE) on PTSD symptoms (as measured by the Clinician Administered PTSD Scale (CAPS)) more than placebo augmentation over 9 weeks of treatment, and 2) VRE will be associated with more improvement than PE (CAPS) over 9 weeks of treatment. The exploratory hypotheses are: 1) there will be an interaction between DCS and mode of exposure therapy such that DCS + VRE will be more effective at reducing PTSD symptoms over the first 5 sessions than the other treatment combinations 2) DCS (relative to placebo) augmentation of exposure therapy will be greater for participants with the BDNF single nucleotide polymorphism (SNP) (Val66Met) than for participants without this SNP, and 3) change in startle response will be associated with change in PTSD symptoms post-treatment.

2.2. Study design

This is a 2 (DCS vs PLA) x 2 (VRE vs PE) double-blind treatment study for combat-related PTSD. Eligible participants were active duty military personnel, reservists, National Guard, veterans, and civilians who experienced traumatic events during their deployment to Iraq or Afghanistan. Participants received 9 sessions of exposure therapy, randomly assigned to either VRE or PE, with all exposure sessions preceded by a pill 30 min prior to the start of the exposure therapy. A blind, independent evaluator assessed PTSD and other significant indicators of psychopathology using structured clinical interviews and self-report measures with well-established psychometric properties at pre-, mid-, and post-treatment, and 3-month follow-up. All participants underwent psychophysiological assessment at pre-, post-treatment and 3-month follow-up and provided a saliva sample for DNA analysis.

This design allows several important comparisons to be made including a direct comparison of VRE versus PE and a direct test of DCS as a facilitator of exposure therapy. In addition, this design will allow the examination of whether any effects of DCS differ across modes of exposure therapy and whether genetic markers and psychophysiological indicators serve as moderators and mediators of the response to treatment and as secondary outcome measures.

2.2.1. Study sites

Participants were recruited at three geographically diverse sites: Weill Cornell Medical College (WCMC) (lead site) in Manhattan and White Plains, NY, National Intrepid Center of Excellence (NICoE), and Walter Reed National Military Medical Center (WRNMMC) in Bethesda, MD, and Veterans Administration Long Beach Healthcare System (LBVA), in Long Beach, CA. This multisite design was used to increase generalizability by covering diverse geographic areas of the country and recruiting from different types of treatment facilities, including a civilian medical center, a Veteran's Administration (VA) location, and an active duty military base.

The study was approved by each site's Institutional Review Board (Weill Cornell IRB number 1005011047, WRNMMC IRB number 361712, LBVA IRB number 1083) and the Office of Human Research Protection, U.S. Army Medical Research and Materiel Command (USAMRMC). It is also registered at [Clinicaltrials.gov: NCT01352637](https://clinicaltrials.gov/ct2/show/study/NCT01352637).

2.2.2. Study population and recruitment

The study population was comprised of U.S. military service members of any duty status and veterans of any discharge status who served in Iraq or Afghanistan (Operations Iraqi Freedom and Enduring Freedom (OIF/OEF), or other later operation), regardless of rank, race, age, gender, or sexual orientation. The study was also open to civilians exposed to war zones in Iraq and Afghanistan (e.g. contractors, journalists). Study inclusion/exclusion criteria are listed in [Table 1](#).

Participants were identified by Institutional Review Board-approved fliers, clinician letters, direct recruitment at military and veterans' events, as well as Craigslist postings, newspaper ads, radio ads, and

Table 1
Inclusion and exclusion criteria.

Inclusion criteria:	
1	Diagnosis of OEF-OIF (Operations Enduring Freedom or Iraqi Freedom, or other later operations) Combat Related PTSD
2	Female participants of childbearing potential must agree to use an effective method of birth control (i.e., oral contraceptive, Norplant, diaphragm, condom, or spermicide) during the course of the study, or to remain abstinent from sex, to ensure they do not become pregnant during the course of the study
3	Ability to provide informed consent and function at an intellectual level sufficient to allow accurate completion of all assessment instruments
4	Participants must be literate in English
5	Participants must be medically healthy and willing to take the study medication
6	Participant's trauma must be consistent with available VRE stimuli
Exclusion criteria:	
1	Lifetime or current diagnosis of schizophrenia or other psychotic disorder, bipolar disorder
2	Participation in a clinical trial during the previous 3 months
3	Current evidence or history of significant unstable medical illness or organic brain impairment, including stroke, CNS tumor, demyelinating disease, cardiac, pulmonary, gastrointestinal, renal, or hepatic impairment
4	Participants who in the investigator's judgment pose a current suicidal or homicidal risk
5	Alcohol, medication, or substance dependence within the past 90 days other than nicotine or caffeine
6	Treatment with any other concomitant medication with primarily CNS activity, or treatment with any medication that the PI judges not acceptable for this study
7	History of seizures
8	Pregnancy or lactation

Facebook study announcements. Participants interested in the study were screened via telephone for initial eligibility. Eligible participants completed an in-person pre-treatment assessment. Participants were reimbursed \$50 for this assessment and \$75 for each additional assessment during the course of the study (two mid-intervention assessments; post-treatment assessment and 3-month follow-up). Travel to treatment sessions was reimbursed as needed for hardship on a case by case basis.

2.3. Study assessments

Written informed consent was obtained from each potential study participant prior to the study pre-treatment assessment. All participants were informed as to the purpose, potential risks and known benefits of the study.

2.3.1. Psychiatric assessment

An independent evaluator assessed symptoms of PTSD and other psychopathology using structured clinical interviews and self-report measures with well-established psychometric properties.

Index trauma, PTSD diagnosis, and symptom severity:

1. Clinician Administered PTSD Scale (CAPS) for the DSM-IV [34]. The CAPS, a structured clinical interview designed to assess the 17 DSM-IV PTSD symptoms, provides categorical ratings of diagnostic status as well as a quantitative index of symptom severity. The CAPS total severity score is based on response to the 17 items that assess the frequency and intensity of current PTSD symptoms. Symptom severity was assessed separately for past month and past week time frames.
2. Self-reported PTSD Symptom Scale (PSS) [35] and the Posttraumatic Stress Disorder Checklist (PCL) [36]. The PSS and PCL correspond to the PTSD symptoms listed in DSM-IV, are sensitive to treatment effects, and are highly correlated with the CAPS and with measures of PTSD-related psychopathology [35,36].

Major depressive disorder (MDD) and other psychiatric diagnoses:

1. Mini International Neuropsychiatric Interview (MINI). The MINI is a short, structured diagnostic interview designed for DSM-IV and ICD-10 psychiatric disorders [37].
2. The Beck Depression Inventory (BDI) [38]. The BDI is a 21-item self-report measure widely used in diverse populations, including trauma survivors, and shown to be sensitive to treatment effects on depression.

Participant characteristics:

1. Demographic characteristics (age, race, ethnicity, education level, marital status, employment status, and living situation), basic medical history, deployment history, and current and prior PTSD treatment was assessed using the Participant Profile Form developed specifically for this study.
2. Pre-deployment/prewar, deployment/war-zone, and post-deployment/postwar risk and resilience factors for stress-related illnesses were assessed using the Deployment Risk and Resilience Inventory (DRRI) [39], which is content-valid for contemporary deployments.
3. The Defense and Veterans Brain Injury Center (DVBIC) TBI Screening Tool assesses Traumatic Brain Injury [40].
4. Lifetime trauma history and childhood trauma history was assessed using the Trauma History Questionnaire (THQ) [41] and Childhood Trauma Questionnaire (CTQ) [42].
5. Impulsive personality traits was assessed using the Barratt Impulsivity Scale (BSI-11) [43].
6. Propensity to experience presence while in a virtual reality simulation was assessed using the Immersive Tendencies Questionnaire [44].
7. Quality of Life Inventory (QOLI) assesses positive mental health, well-being and quality of life [45].
8. Participant treatment preference (VRE vs. PE) and strength of preference (Likert scale ranging from 0 to 10) was measured using the Patient Preference and Strength of Preference form developed for this study.

Therapy process measures:

1. The Client Expectancy Questionnaire (CEQ) was used to assess therapy credibility and client expectancy [46].
2. Intent to Attend measure was used to assess participant's willingness to attend the next study session and to estimate attrition.

The complete list of measures used in the study is listed in [Table 2](#).

2.3.2. Medical clearance

During the pre-treatment visit, the study physician at each site reviewed each participant's medical history to ensure they had no contraindications to receiving DCS. Participants taking psychotropic medication must have been on a stable dose for at least 2 months. Female participants of childbearing age performed a urinary pregnancy test at the beginning of the study and in each follicular phase visit after starting the study medication.

Table 2
Assessment schedule.

Measure	Pre-treatment	Mid-treatment	Post-treatment	3-month follow-up
Interviews:				
Clinician Administered PTSD Scale (CAPS)	X	X	X	X
Mini International Neuropsychiatric Interview (MINI)	X		X	X
Demographic Participant Profile Form	X			
DVBIC TBI Screening Tool	X			
Trauma History Questionnaire (THQ)	X		X	X
Blinded medication/treatment check		X	X	
Self-report measures:				
PTSD checklist (PCL)	X	X	X	X
PTSD Symptom Scale-SR (PSS)	X	X	X	X
Beck Depression Inventory (BDI)	X	X	X	X
Intent to Attend	X	X	X	X
Deployment Risk and Resilience Inventory (DRRI)	X			
Childhood Trauma Questionnaire (CTQ)	X			
Barratt Impulsivity Scale (BSI-11)	X			
Immersive Tendencies Questionnaire (ITQ)	X			
Patient Treatment Preference and Strength of Preference	X			
Quality of Life Inventory (QOLI)	X		X	X
Client Expectancy Questionnaire (CEQ)	X		X	X
Client Satisfaction Questionnaire (CSQ)		X	X	X
Biological measures:				
Startle assessment	X		X	X
Cortisol	X		X	X
DNA extraction	X			

Note: Identical mid-treatment assessments were conducted after sessions 4 and 6.

2.3.3. Genetic assessment

A saliva sample for DNA extraction was collected from every consenting participant. Participants were asked to rinse their mouths with water and then salivate into a cup (~4 cc total). Saliva samples were collected using the Oragene system (DNA Genotek) which provides a number of benefits for a study with the proposed design. Samples can be stored at room temperature for extended periods of time (including for future use in PTSD research, contingent upon participants' consent). Samples were processed in batches of 24, which is the capacity of a standard benchtop microcentrifuge – the rate limiting step in sample processing. Taqman 5' exonuclease assays (Assay on Demand, ABI) were used to genotype DNA samples at BDNF Val66Met (rs6265) and other candidate genes.

2.3.4. Psychophysiological assessment

During the psychophysiological assessment participants were exposed to a fear conditioning and extinction paradigm and combat-related virtual imagery task. The combat scenes included those most commonly experienced by OIF/OEF service members. The virtual scenes were standardized so that each participant was assessed in a uniform manner utilizing the same environment with the same stimuli presented [22,23]. Visual stimuli were presented on a computer monitor and acoustic stimuli were presented with headphones. The acoustic startle probe was a 40 ms white noise burst of 106 dB with instantaneous rise time. Psychophysiological measurements were acquired using Biopac MP150 for Windows (Biopac Systems, Inc.) and included electromyographic (EMG) recordings of the right orbicularis oculi eye blink muscle, skin conductance level (SCL), and electrocardiogram (ECG). All data were sampled at 1000 Hz and exported to Mindware (Mindware Technologies, Inc.) for filtering and analyses.

2.3.4.1. Fear conditioning and extinction. The following methods allowed us to assess fear acquisition, conditional discrimination to assess fear inhibition to learned safety, and within-session extinction, as well as participant awareness of reinforcement contingencies in the experiment. The aversive unconditioned stimulus (US) was an air blast directed to the larynx, with an intensity of 140 p.s.i., and duration of 250 ms, as described in our previous human fear conditioning studies

[47,48]. Air blasts were delivered by a compressed air tank connected to polyethylene tubing and controlled by a solenoid switch. Conditioned stimuli (CS) were colored shapes presented on a computer monitor. The colored shapes were counterbalanced across subjects. Stimuli were presented using SuperLab 5.0 for Windows and responses were recorded on a response pad RB-730 (Cedrus, Inc.).

A conditional discrimination paradigm (termed AX+/BX-) described in our previous work [47] was followed by extinction to the AX+ trials (see Fig. 1). During the fear acquisition phase of the paradigm, the CS was a simultaneous presentation of two shapes with a "+" sign between them— one of the shapes was either A or B, and the other was X. The AX+ compound was the reinforced CS+, which was paired with the US 100% of the time. The BX- compound stimulus was never paired with the US, making it the non-reinforced CS-. The color and shape of A and B differed, but the "X" cue remained the same across both presentations. This conditional discrimination task (where danger vs safety was conditional on the presence of either A or B, respectively) was specifically designed in order to test the ability of a learned safety cue to inhibit the conditioned fear response. It has been shown to be sensitive to treatment effects [33].

The session began with a habituation phase consisting of six acoustic startle probes presented alone (noise alone (NA) trials) to reduce initial startle reactivity; this phase was followed by a stimulus pre-exposure phase during which the participant saw the shapes (A, B, and X), unpaired with the US. The acquisition phase consisted of three blocks with four trials per block of AX+, BX-, and NA trials, for a total of 12 conditioning trials of each type. Immediately after the acquisition phase, fear inhibition was assessed during a transfer test, during which the A and B cues were presented together as an AB compound for the first time. The transfer test included only three AB trials to minimize extinction effects and capture immediate transfer of safety. Ten minutes after the transfer test, the extinction session began, which included four blocks with four AX, BX, and NA trials in each block. During extinction neither the AX nor BX compound stimuli were paired with the air blast US. The stimuli were presented on the screen for 6 s and the intertrial intervals (ITIs) as well as interblock intervals were randomized in duration ranging from 9 to 22 s.

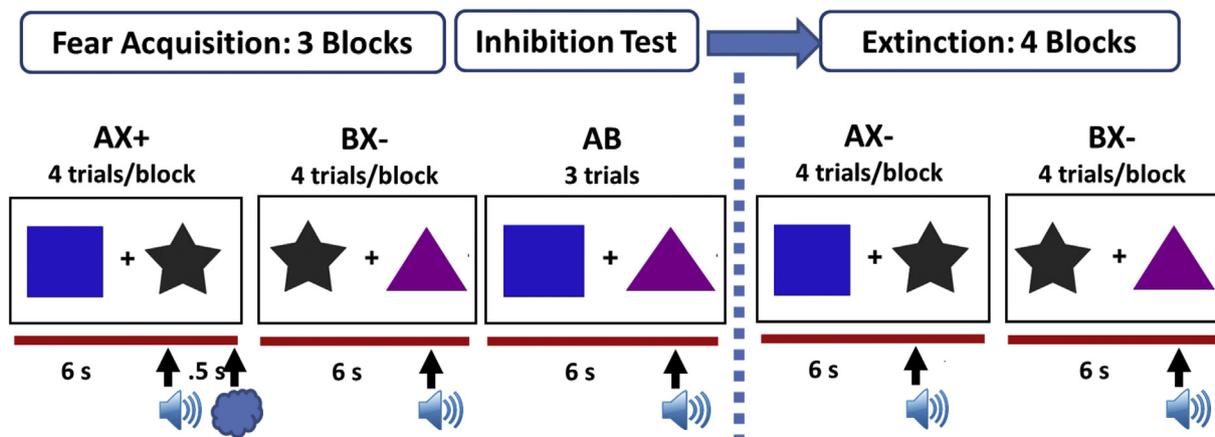


Fig. 1. Fear conditioning and extinction.



Fig. 2. Psychophysiological reactivity to virtual combat clips.

2.3.4.2. Psychophysiological reactivity to virtual combat imagery. The virtual trauma reminders task has been used previously in our lab and has shown pre-post treatment changes in patients with PTSD [23] (see Fig. 2). The VR assessment included three standardized 2-min combat-related scenes presented from a first-person point of view. The session began with a 30 s presentation of a neutral blue square during which baseline measures were collected. The blue screen was repeated in between each combat scene and two startle probes were delivered during each blue screen. The first VR scene depicted military personnel at the gunner position on the roof of a Humvee. Combat-related stimuli including smoke, gunfire, explosions, and roadside insurgents presented in an ascending order of intensity. Six startle probes were delivered throughout the video scene at time points in which combat-related audio stimuli were minimal. The second VR scene depicted a soldier's position within the cabin of a humvee, and the third a soldier's point of view as he/she walks through the streets of a middle eastern city resembling Baghdad. Startle probes were again presented when other combat-related auditory stimuli were minimal.

Cortisol Collection: Salivary cortisol samples were collected at four points during the psychophysiological assessment (prior to assessment, between the fear acquisition and extinction phase, following the assessment, and 15 min post-assessment). Saliva was collected using the Salivette passive drool method (www.sarstedt.com). Samples were stored in freezers at -80°C and processed in batches of 37, using commercially available enzyme immunoassay kits (Salimetrics).

2.4. Study intervention

2.4.1. Intervention

The study intervention was delivered in nine 90-min individual weekly sessions to both therapy conditions (VRE and PE). Across therapy conditions, the sessions were identical in timing and structure except for the mode of delivery of stimuli (virtual reality exposure vs. imaginal exposure). The study intervention followed guidelines for exposure therapy for PTSD. The first two sessions were the *Educational Sessions* and began with an overview of the intervention and a general rationale for exposure. The therapist gathered information focusing on the participant's symptoms, details of the trauma, history of previous trauma and subsequent trauma, and social and occupational functioning. The therapist provided an explanation of PTSD, discussed common reactions to trauma, discussed a rationale for the intervention, and provided a description of the intervention. A slow breathing exercise was taught in the context of its potential use for relaxation induction. The remaining seven sessions consisted of either VRE or PE and discussion of these experiences. The 90-min session consisted of approximately 15 min of checking in with the participants about their functioning and anxiety since the last session, 30–45 min of exposure to their traumatic memories, and approximately 30 min of processing and discussion about the material from the exposure. The therapist asked the participant to give SUDS (Subjective Units of Distress Scale, 0 = no anxiety and 100 = maximum anxiety) ratings as an indication of level of anxiety. SUDS ratings were recorded at the beginning, end, and peak only during the exposure component of the treatment sessions. During exposure, the therapist asked specific questions to clarify the participant's thoughts, feelings, and physical reactions while revisiting the trauma to facilitate confrontation with fear-evoking cues. The parts of the scenario that produced the most anxiety for the participant were identified and emphasized in repeated exposure. Participants recounted the traumatic memory as many times as possible within the 30–45 min time frame. Most participants recounted the traumatic incident approximately 3 times per session. As the number of sessions was limited, exposure was limited to the 3 most traumatic events. The therapist made appropriate comments and encouraged continued exposure to facilitate reduction in anxiety. After the exposure, the therapist encouraged the participant to discuss reactions to revisiting the trauma memory and related thoughts and remembered details ("processing"). Through these discussions, the participant learned to identify, evaluate, and modify disturbing thoughts and feelings and developed more realistic beliefs about personal coping ability and the dangerousness of the world. By the 5th session, exposure focused on "hot spots," or stimuli from the trauma memory that caused the highest anxiety. In vivo homework was not assigned as participants took the study drug only at the treatment sessions where exposure therapy was conducted, and we

wished to minimize the possibility of exposure occurring outside of the medicated state.

2.4.2. Study drug

Beginning at session 3 (the first exposure session), participants were administered a pill (DCS or PLA) upon arrival in the clinic and completed questionnaires and assessments while they waited. The DCS and placebo capsules were identical in size, shape, and form. The exposure session began 30 min after taking the pill. DCS has been FDA approved for approximately 50 years, initially for the treatment of tuberculosis, and then as a cognitive enhancer in several clinical trials over the last decade. No adverse events have been reported in any studies that use low-dose DCS in the treatment of psychiatric conditions [16,23,49–52], and particularly when combined with exposure therapy [16,23].

2.4.3. Prolonged exposure therapy (PE)

After a brief check-in, the participant was instructed to revisit the trauma memory as vividly as possible and to recount it aloud in the present tense for 30–45 min. Participants were instructed to close their eyes and to vividly imagine the scene. The PE treatment manual is widely available [53]. While in-person sessions followed the standard PE protocol, imaginal and in vivo homework were not assigned.

2.4.4. Virtual reality exposure therapy (VRE)

During the VRE sessions, the participant wore an eMagin Z800 Head Mounted Display (HMD) that included separate display screens for each eye, integrated head-tracking, and stereo earphones. The participant was presented with a computer-generated view of a Virtual Iraq/Afghanistan environment that changed in a natural way with head and body motion. The Virtual Iraq/Afghanistan software and environment models were constructed with design input from OIF/OEF veterans and clinicians who used earlier versions of the software. A handheld controller allowed the participant to move forward and navigate within the environment at his/her own pace. In the virtual environment, the participant could drive a Humvee down a desert highway either alone or in a convoy or navigate on a dismounted patrol through Iraq/Afghanistan-like city scenes (see video 1). Trigger stimuli options included sounds of weapons fire, explosions, incoming mortars, helicopter flyovers, vehicle noise, wind, human voices, and radio, and visual stimuli such as night vision, wounded civilians and combatants, and wrecked vehicles. Tactile stimuli (i.e., vibration) was delivered through a raised floor platform with subwoofer speakers attached through which the environmental sounds were delivered by an audio amplifier. The therapist used a clinician interface control panel to deliver or remove trigger stimuli presentations via a standard personal computer that ran the simulations. While the HMD occluded the participant's view of real-world stimuli, the clinician communicated with them via a head-mounted microphone and earphones. The participant was asked to put on the HMD when the exposure portion of the session began and the scene was presented that most closely matched the traumatic incident (e.g., humvee, convoy, city). The therapist asked the participant to recount the trauma memory, following guidelines for standard exposure therapy, while immersed in the virtual environment. The therapist simultaneously viewed the participants' real time perspective of the same virtual environment in which they were interacting on a separate computer monitor. This enabled the therapist to comment appropriately and attempt as much as possible to match virtual stimuli to those that the participant was describing. The participant was asked to remove the HMD at the end of the exposure portion. The VRE sessions followed the VRE therapy manual developed by the study authors [54].

2.5. Procedure

2.5.1. Randomization

Eligible participants (i.e. those who met all inclusion criteria and no

exclusion criteria) were randomized using a 1:1:1:1 allocation ratio, equally allocating participants in each of 4 treatment arms and in levels of exposure therapy (VRE vs. PE) and augmentation (DCS vs. PLA). Randomization was stratified by MDD and site to ensure equal allocation across treatment groups. Randomization was conducted by the study statistician. Randomization lists with both the medication and treatment allocation were sent directly to the Investigational Drug Pharmacy personnel at each site (VRE/DCS, VRE/PLA, PE/DCS, PE/PLA). Randomization lists with treatment allocation only (MDD+/VRE, MDD+/PE, MDD-/VRE, MDD-/PE) were sent to the study coordinator at each site. The site coordinator then assigned each eligible participant to the treatment group indicated on the randomization list. This information was then transmitted to the pharmacy, where the participant was matched with the medication allocation based on the study ID number. Randomization procedures occurred on the day before the first study visit.

2.5.2. Assessment during treatment

All participants were assessed after taking the study medication but before the therapy session began with self-report PTSD measures (PSS and PCL) and a depression measure (BDI). Intent to Attend the next assessment session was completed by the participant and reviewed by the therapist at each session [55] and used to gauge potential attrition. The therapist administered the 18-item Side Effect Screening Checklist to identify possible medication-related side effects and specific adverse symptoms. Participants were monitored for anxiety during the exposure portion of the treatment session via SUDS ratings in which 0 indicates no anxiety and 100 indicates maximum anxiety. SUDS ratings were recorded at three times (beginning, end and peak) during exposure. The therapist noted the exposure, the virtual environment, and cues used in the session. Lastly, the therapist assessed participant and therapist beliefs about medication assignment (active pill vs. PLA). In addition, after session 3, 6, and 9, participants completed the Immersive Tendencies Questionnaire [44] to measure immersion in exposure therapy. Participants who received the VRE therapy completed the Presence Questionnaire [44] to assess presence in a VR environment.

2.5.3. Baseline assessment

The independent assessor, a doctoral-level psychologist blind to treatment condition, assessed symptoms of PTSD and other psychopathology using the CAPS (past month and past week) and the MINI, as well as the self-report measures described above.

2.5.4. Mid-treatment assessments

The independent assessor administered CAPS (past week) after sessions 4 and 6. They also completed the Blinded Treatment Check Form to assess whether the blind (VRE or PE treatment) was broken at any time. Participants completed self-report measures of PTSD (PSS and PCL), depression symptoms (BDI), Intent to Attend, and Client Satisfaction Questionnaire (CSQ).

2.5.5. Post-treatment assessment

The post-treatment assessment paralleled the baseline assessment. A blinded assessor administered CAPS (past week), changes in MDD and other diagnoses present at pre-treatment (MINI), new traumatic events experiences since the start of the study (THQ), and changes in any concomitant medications. Assessments occurred in person or via telemedicine if participants were unable to come in person. The Blinded Treatment/Medication Check Form was completed. Participants completed self-report measures of PTSD (PSS and PCL) and depression symptoms (BDI). In order to assess functional change after the intervention and reactions to the intervention, participants completed the Quality of Life Inventory (QOLI), Client Expectancy Questionnaire (CEQ) and Client Satisfaction Questionnaire (CSQ). Participants underwent the psychophysiological assessment.

2.5.6. Three-month follow-up

A blinded assessor administered the CAPS (past month and past week), assessed for changes in MDD and other diagnoses present at pretreatment (MINI), as well as new traumatic events experienced since the end of the study (THQ). Any changes in medications were determined. Participants completed the same self-report measures as at posttreatment. Participants repeated the psychophysiological assessment.

2.6. Data collection and management

Weill Cornell is the data management and statistical analysis core for this study. To preserve confidentiality and privacy, each participant was given a unique set of identification numbers (screening ID and study ID), which were used on all forms. Participant identifiers were maintained at each site and not shared with the data management site. All study data was entered by assessors, therapists, and study participants directly into the research data management system, REDCap [56]. REDCap is a Hypertext Preprocessor (PHP)-based system, developed by Vanderbilt University and currently managed and updated through a national consortium, the Clinical and Translational Science Centers, which was created and is maintained by the National Institutes of Health. REDCap supports the rapid setup of secure, web-based study-specific database systems and associated forms. It provides full field validation capabilities (customized to each study), import/export (including export to common statistical packages such as SAS, SPSS, and Excel), and file upload/management functions. It includes a complete suite of features to support HIPAA compliance, including a full audit trail, user-based privileges, and integration with the institutional server. Study data are collected and managed using REDCap hosted at the Weill Cornell Medical College Clinical and Translational Science Center.

Participant's saliva samples for cortisol analysis were coded and stored for 6–12 months in a secure freezer at -80°C at each site. Samples were shipped by FEDEX on dry ice and processed at Weill Cornell Medical College Clinical and Translation Science Center. Saliva samples for genetic analysis from other sites were stored at room temperature and shipped to Weill Cornell Medical College for processing in batches.

2.7. Cross site calibration

Calibration of clinical, psychophysiological, and genetic data collection procedures was conducted prior to beginning the protocol (in the first 6 months of the study) at each site and periodically through the trial. The first 6 months were dedicated to training personnel and standardizing the assessment and treatment procedures. Clinicians participated in an intensive 2-day training meeting led by the senior investigators with expertise in the assessment methodology and treatments. Training in the study treatment protocol consisted of a review and discussion of the PTSD literature, a review of the treatment manual and viewing videotaped sessions (from participants who consent) of VRE and PE sessions. Therapists received supervision for each session during training, and then for their first randomized VRE and PE participants. Thereafter, supervision was conducted by weekly conference calls with all therapists across sites. Therapists were able to request assistance and individual supervision as needed for difficult cases, and supervisors were able to initiate individual supervision with a therapist based on their observation of session videotapes, material introduced in conference calls, or feedback from the protocol adherence monitors. Twenty percent of all therapy session videotapes were randomly selected for treatment adherence ratings and sent to a PE expert and a VRE expert, respectively, who were independent of the study. The monitors joined the weekly calls periodically to discuss the adherence ratings. Likewise, 10% of all study assessments were randomly selected for interrater reliability. Additionally, issues around the study

administration, conduct, and recruitment were addressed in weekly Principal Investigators conference calls and separate study coordinator calls.

3. Statistical analysis

Baseline demographic and clinical characteristics will be examined. Measures of central tendency (mean, median) and variability (standard deviation, minimum and maximum) will be estimated on each continuous measure; proportions estimated for categorical variables. Graphical displays (e.g., histograms and boxplots) will be produced. Transformations will be used when distributional assumptions are not fulfilled for inferential tests. The treatment groups will be compared on baseline demographic and clinical variables using ANOVA or Kruskal-Wallis tests for continuous variables; chi-square tests for categorical variables. If significant baseline group imbalance is detected on a particular variable, that variable will be included as a covariate in the inferential analyses if it is correlated with outcome at a level of 0.30 or higher ($r \geq 0.30$). In a similar manner, dropouts and completers will be compared on baseline variables using ANOVA, Kruskal-Wallis tests, or chi-square tests.

3.1. Primary analyses

The primary hypotheses will be tested in the following manner. Mixed-effects linear regression analysis [57] will examine the repeated assessments of CAPS (past week) over the 9-week trial. There will be 4 assessments of CAPS (baseline, after sessions 4, 6, and at post-treatment assessment). The mixed effects model will include a random intercept and slope over time and fixed effects for exposure therapy (VRE vs. PE) or augmentation (DCS vs. PLA), with site and MDD diagnosis included in both models. Likelihood ratio tests for each model will examine the incremental contribution of the augmentation (DCS vs. PLA) by time interaction, and the incremental contribution of the exposure therapy (VRE vs. PE) by time interaction, respectively. Post hoc comparisons within significant interaction effects will be conducted using univariate *t*-tests on the model estimated means. Standardized effect sizes (ES) will be computed by dividing model estimated between-group differences at posttreatment by the common standard deviation of the measure changes scores baseline-posttreatment. A multiplicity adjusted two-tailed alpha level of 0.025 will be used for each of the two primary analyses. Site by exposure therapy and site by augmentation interactions will also be examined and included in the model if significant at the 0.10 level. Likewise, MDD diagnosis by exposure therapy and MDD diagnosis by augmentation interactions will be included in the model if significant at the 0.10 level. In addition, likelihood ratio tests will be used to compare the model fit with that having a first-order autoregressive (AR1) covariance structure [58]. The primary hypotheses will be tested adhering to the principle of intention to treat. That is, each participant will be classified in the analyses based on randomized group assignment. The mixed effects models will include data from participants with incomplete data. Mixed models yield valid inferences assuming ignorable attrition (i.e., accounted for by measures of covariates or the dependent variable measured prior to dropout). A pattern mixture model [59] will be used to examine response to treatment among participants with various dropout patterns. It will be implemented in the mixed-effects framework described by Hedeker and Gibbons (1997) [60] in which subjects are classified by attrition pattern (e.g., early dropout, middle dropout, late dropout, completer). If the sensitivity analysis show results that are inconsistent with findings of the primary proposed analyses, the inconsistency will be reported. Finally, we made every effort to continue assessments for the entire course of randomized treatment, even among those who failed to comply with randomized treatment assignment or had to leave study assigned treatment [61].

3.2. Secondary analyses

Analyses other than the co-primary hypotheses will use an unadjusted two-tailed alpha level of 0.05. The effect of treatment on self-report measures of change in PTSD symptomatology (PSS, PCL) and depressive symptomatology (BDI) will be analyzed in a similar approach as the CAPS.

3.3. DCS and mode of exposure therapy interaction

The testing of the interaction hypothesis will build on the mixed-effects linear regression models described above in that it will include a random intercept and slope and fixed effects for exposure therapy (VRE vs. PE), augmentation (DCS vs. PLA), site, MDD, and any of the significant interactions identified in the co-primary analyses. Covariates included in the co-primary analyses will likewise be added to the model. A likelihood ratio test will then examine the incremental contribution of the exposure therapy by augmentation interaction.

3.4. Genetic markers as moderators of response to DCS

The analyses of the moderating effects of genetic markers (BDNF SNP (Val66Met)) are exploratory and, as recommended by Kraemer et al. [62], will focus on the magnitude of the effect. They will not involve significance testing. In contrast to repeated dependent measures analyses proposed above, a fixed-effects approach where the dependent variable is the CAPS pre-post change will be used. We will compare the between augmentation group (DCS vs. PLA) effect sizes (Cohen's *d*) for those with and without the respective genetic marker. These analyses, which are exploratory and require pre-post change scores, will only include participants who complete the 9-week trial. A moderating effect would be deemed present if a substantial difference in effect size is observed, yet it would be interpreted as preliminary. Results from these exploratory analyses could be used to guide the design of future randomized controlled trials (RCTs) of DCS (e.g., inclusion/exclusion criteria based on the moderator data) that would focus on those participants most likely to respond to DCS.

3.5. Psychophysiological data analysis

This exploratory hypothesis will be tested in multiple linear regression analyses. The dependent variable will be CAPS (pre-post change). The independent variables will include augmentation (DCS vs. PLA), exposure therapy (VRE vs. PE), and site. Four separate regression models will each examine one of the measures of startle response (pre-post change) as an independent variable (Startle Amplitude, Fear-Potentiated Startle, Discrimination, and Transfer of Inhibition). The incremental contribution of the interaction of each startle variable with augmentation will be then examined in subsequent models. The $R^2_{\text{increment}}$ will quantify the proportion variance in CAPS change that is accounted for by each interaction. As described above, these exploratory analyses will focus on the magnitude of the association.

3.6. Statistical power/sample size

The sample size was planned to provide adequate power (≥ 0.80) for testing the two primary hypotheses. We proposed to enroll a total of 300 participants (150 for each level of each factor) based on the Diggle [63] algorithm for sample size requirements for longitudinal models and the multiplicity-adjusted two-tailed alpha-level of 0.025 to accommodate the two primary hypotheses [64]. We assumed the intraclass correlation coefficient (ICC) = 0.60; and in an effort to account for attrition, we assumed that each participants will provide 3 of the 4 planned observations. A sample size of 150 per group provided 80% power to detect an effect size of 0.30 standard deviation units. Such an effect size is necessary because we plan to compare two active

therapies. An effect size of this magnitude corresponds to a group difference of 9 units on the CAPS [65] (Standard Deviation (SD) 30), which we consider clinically meaningful for each of the experimental factors: exposure therapy (VRE vs. PE) and augmentation (DCS vs. PLA).

3.7. Data monitoring board

A Data Safety Monitoring Board (DSMB) was established at the lead site (WCMC) before the start of the study. The board periodically reviewed study recruitment, participant retention and safety-related issues. In addition, an independent medical monitor was established to review any study related adverse events.

4. Discussion

Despite recent advances in the understanding of PTSD, effective empirically validated treatments for combat-related PTSD remain elusive. Most military personnel, regardless of duty or discharge status, do not seek professional mental health treatment with only 23–40% of those who need treatment seeking it [1]. A report issued by the U.S. Department of Veteran Affairs indicates that only 26.1% of post 9–11 veterans seek treatment at a VA facility [66]. Compliance, stigma, and drop-out remain significant threats to treatment integrity for those who seek any PTSD treatment. Moreover, there are currently no biological markers or genetic tests for PTSD as there are for other medical conditions (e.g., certain cancers) that allow for informed treatment selection. Thus, we cannot predict which of the few empirically validated treatments will work for whom. In this study, we seek to determine if certain genetic markers will predict treatment response, which may lead to differential therapeutics for PTSD. Stigma and access also hinder effective service delivery. Finally, the avoidance inherent in PTSD compounds these deleterious problems.

The current study seeks to use the one treatment, exposure therapy, noted by the IOM's reports [5,6] and other professional guild associations [67,68] to have substantial research evidence in support of its use in other trauma populations. The proposed design has several advantages: all participants received an active, effective treatment and thus no participant received a treatment with completely unknown efficacy. We will both test exposure therapy in military personnel of any duty status and enhance it with additional interventions (i.e., virtual reality enhanced exposure therapy and a novel pharmacologic agent, DCS).

Results obtained through this study will allow several important comparisons to be made including: 1) a direct comparison of VRE versus PE and 2) a direct test to determine if DCS can facilitate exposure therapy for combat-PTSD. This may allow for the development of a brief, effective treatment that can be delivered faster and more efficiently and lead to an increase in treatment compliance. Determining if the effects of DCS differ across specific types of exposure therapy informed by the genetic findings may synergistically contribute to a differential therapeutic for PTSD. Importantly, the findings may lead to the development of the first human genetic test that could guide treatment selection, ultimately allowing for more tailored treatment plans in the future. Currently there are no genetic or non-genetic biomarkers for assessing treatment response to any psychiatric disorder. Specifically, findings from this study may lead to the development of the first human genetic test that could guide treatment with this SNP to therapeutic strategies. Tailored treatment plans may increase compliance, decrease both short and long term disability and lost productivity, and ultimately decrease the stigma associated with mental health treatment.

We treated any servicemember or veteran deployed under OIF/OEF regardless of military branch or duty status, as long as they met study criteria. We believed that this was feasible because each of the medical centers involved in this proposal were in major metropolitan areas

serving distinct geographic regions (Northeast, Mid-Atlantic, and southern California) without any overlap.

If effective, the use of DCS to enhance exposure therapy could impact the quality of life of active duty military and veterans suffering from PTSD. The pharmacologic agent, DCS, was administered weekly 30 min before the treatment session, in low doses. The dose used has not been associated with any side effects. If effective, DCS may replace the use of agents such as anxiolytics, Selective Serotonin Reuptake Inhibitors (SSRIs), and sedatives that are often associated with significant side effects. Some of the known side effects of the drugs currently in use may impair work performance (e.g., decreased reaction time associated with anxiolytics and sedatives) and in the case of active duty military personnel, prevent the individual from performing their normal work duties (e.g., deployed active duty military). Additionally, these drugs may impair quality of life (e.g., sexual side effects associated with SSRIs) which often lead to noncompliance with the pharmacologic regimen.

VRE and DCS may reduce the time in treatment thereby decreasing the period of disability often associated with PTSD as well as decreasing the cost of disability. Shortening the treatment would also lower the cost of the treatment itself and likely reduce drop-outs.

Many elements of the treatment may increase compliance with treatment. The use of VR may improve the “face” validity of the treatment, especially for younger veterans and servicemembers who have grown up playing video games. The use of a medication to hasten treatment response may increase compliance by more rapidly reducing the disabling symptoms, such as avoidance, which often interfere with treatment compliance (i.e., those with PTSD often avoid reminders of their trauma including talking about it; thus, treatment itself falls victim to the participant's symptoms). Additionally, since the design of the current study stratifies the sample by the diagnosis of major depressive disorder, results may inform the use of VRE and PE in trauma populations with this common co-morbid diagnosis.

Shortening treatment length and eliminating significant work-impairing side effects may allow active duty military to continue to work during treatment and, if redeployed, to return to their pretrauma “peak performance” capacity thereby contributing to the maintenance of the strongest possible military capability.

If successful, use of genetic testing to develop a differential therapeutics for PTSD treatment could have a very significant impact on treatment planning. Currently there are no reliable means to predict response to treatment for PTSD. Use of a genetic screening test to match participants to the treatments that are likely to be most effective for them would have an impact on treatment response, compliance, and thereby impact disability rates and the economics of PTSD (i.e., reduce the cost of treatment and the costs of disability).

In summary, the potential benefits to society of these investigations are huge. PTSD is a major public health problem, with considerable cost to the individual, the family, and the community, and is obviously a major problem in military personnel who experience combat. Since about 70% of people will experience a traumatic event in their life, this knowledge will be helpful to civilians and military personnel alike who cope with trauma. The findings of this study may help those in the military improve overall functioning personally and occupationally. The results of this trial will directly influence the future delivery of services and may help disseminate a standardized treatment protocol as is being done for other psychiatric disorders.

The results of this study may provide the basis for an enhanced but abbreviated, and therefore potentially more cost-effective and tolerable, form of exposure therapy for chronic PTSD sufferers who might not otherwise complete or respond to treatment.

Trial status

Participants were seen from April 1, 2011 through April 5, 2018.

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Author's contributions

All authors made substantial contributions to this manuscript. All authors were involved in drafting the manuscript and critically revising it for intellectual content and accuracy. All authors have approved the final version of the manuscript for publication.

Declaration of competing interest

The authors, with the exception of Dr. Difede, Dr. Rothbaum, and Dr. Rizzo, declare no conflicts of interest.

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