Testing a variable-length Cognitive Processing Therapy intervention for posttraumatic stress disorder in active duty military: Design and methodology of a clinical trial

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ABSTRACT

Combat-related trauma exposures have been associated with increased risk for posttraumatic stress disorder (PTSD) and comorbid mental health conditions. Cognitive Processing Therapy (CPT) is a 12-session manualized cognitive-behavioral therapy that has emerged as one of the leading evidence-based treatments for combat-related PTSD among military personnel and veterans. However, rates of remission have been less in both veterans and active duty military personnel compared to civilians, suggesting that studies are needed to identify strategies to improve upon outcomes in veterans of military combat. There is existing evidence that varying the number of sessions in the CPT protocol based on patient response to treatment improves outcomes in civilians. This paper describes the rationale, design, and methodology of a clinical trial examining a variable-length CPT intervention in a treatment-seeking active duty sample with PTSD to determine if some service members would benefit from a longer or shorter dose of treatment, and to identify predictors of length of treatment response to reach good end-state functioning. In addition to individual demographic and trauma-related variables, the trial is designed to evaluate factors related to internalizing/externalizing personality traits, neuropsychological measures of cognitive functioning, and biological markers as predictors of treatment response. This study attempts to develop a personalized approach to achieving positive treatment outcomes for service members suffering from PTSD. Determining predictors of treatment response can help to develop an adaptable treatment regimen that returns the greatest number of service members to full functioning in the shortest amount of time.

1. Introduction

Combat-related trauma exposures have been associated with increased risk for posttraumatic stress disorder (PTSD) and comorbid mental health conditions (e.g. Ref. [1]). Current estimates of PTSD prevalence in military personnel and returning veterans range from 7 to 20% [2], suggesting a significant need for mental health treatment of this population. Cognitive Processing Therapy (CPT) has emerged as one of the leading evidence-based treatments for combat-related PTSD among military personnel and veterans. Well-designed randomized

Abbreviations

ANT	Attentional Network Task
AUDIT	Alcohol Use Disorders Identification Test
BDNF	brain-derived neurotrophic factor
CANTAB	Cambridge Neuropsychological Test Automated Battery
CAPS-5	Clinician-Administered PTSD Scale for *DSM-5*
CART	classification and regression trees
CPT	Cognitive Processing Therapy
CRDAMC	Carl R. Darnall Army Medical Center
CTQ	Childhood Trauma Questionnaire
CTS-2	Revised Conflict Tactics Scale
DDRI-2	Deployment Risk and Resilience Inventory-2
D-KEFS	Delis-Kaplan Executive Function System
DoD	U.S. Department of Defense
DSI-SS	Depressive Symptoms Index – Suicidality Subscale
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
DSMB	Data Safety and Monitoring Board
GAD-7	Generalized Anxiety Disorder Screener
IAT	Implicit Association Test
ICG	Inventory of Complicated Grief
IE	independent evaluator
IPF	The Inventory of Psychosocial Functioning
IRB	Institutional Review Board
PCL-5	PTSD Checklist for *DSM-5*
LTA	Latent Transition Analysis
LEC	Life Events Checklist
MASQ	Mood and Anxiety Symptom Questionnaire
PE	Prolonged Exposure therapy
PHQ	Patient Health Questionnaire
PROMIS	Patient Reported Outcomes Measurement Information System
PTCI	Posttraumatic Cognitions Inventory
PTSD	posttraumatic stress disorder
RCT	randomized clinical trial
SNP	single nucleotide polymorphism
STAXI-2	State-Trait Anger Expression Inventory-2
STOP	Snoring, Tired, Observed, Blood Pressure Sleep Apnea Screen
STRONG STAR	South Texas Research Organizational Network Guiding Studies on Trauma and Resilience
TRGI	Trauma-Related Guilt Inventory
URICA-T	University of Rhode Island Change Assessment Scale – Trauma
U.S.	United States
UTHSCSA	University of Texas Health Science Center at San Antonio
VA	Department of Veteran Affairs
VR-12	Veterans RAND 12-Item Health Survey
WAI	Working Alliance Inventory
WHYMPI	West Haven Yale Multidimensional Pain Inventory.

clinical trials support CPT as an effective treatment for PTSD and other comorbid conditions in a variety of trauma populations, including sexual abuse survivors [3,4], veterans (e.g. Refs. [5,6]), and active duty military personnel [7,8]. However, rates of remission have been less in veterans and active duty military personnel compared to civilians [9]. In the only published studies of CPT with active duty military, over half of service members retained their PTSD diagnosis after completion of the prescribed 12-session CPT protocol [7,8]. These findings suggest that studies are needed to identify strategies to improve upon outcomes in military populations.

There is existing evidence that varying the number of sessions in the CPT protocol based on the individual's response to treatment improves outcomes. Galovski and colleagues [10] examined a variable-length CPT protocol in a civilian population. They found that more than half of the 100 participants (58%) reached good end state with fewer sessions than the standard 12-session protocol, while 34% took longer to complete the treatment and reach good end state. Only 8% of the participants reached good end state at exactly 12 sessions. Nearly all participants (98%) lost their PTSD diagnosis following treatment.

The current paper describes the design and methodology of a clinical trial testing a variable-length CPT protocol in a treatment-seeking active duty military sample with PTSD to determine if some would benefit from a longer or shorter dose of treatment, and to identify which individuals require more, less, or the standard number of treatment sessions to reach good end state. The primary goal of the study is to improve the efficacy of CPT in this population through a variable-length treatment, specifically targeting "refractory" patients and increasing the focus on overall end-state functioning in addition to loss of PTSD diagnosis. Given that studies using veteran samples have not demonstrated the same levels of treatment success observed in civilian samples, it is conceivable that veterans and military personnel will need a longer dose (more sessions) to reach a good end state. However, there may also be some military personnel who could benefit from treatment more quickly. The study was designed to explore a range of variables that may predict length of therapy and treatment outcome. In addition to demographic and trauma-related factors, other variables include (1) factors related to internalizing/externalizing personality traits, (2) neuropsychological measures including cognitive flexibility and ability to inhibit dysfunctional cognitions, and (3) salivary cortisol and brain-derived neurotrophic factor (BDNF) as predictors of treatment response.

1.1. Research objectives and hypotheses

The primary objective of the study is to evaluate the effectiveness of CPT delivered individually until the service member reaches good end state (up to 24 sessions) and to characterize the distribution of response based on specific predictors of treatment outcome. Good end state is defined as low scores on measures of PTSD and agreement by the patient and therapist that the patient is ready to stop treatment. Hypothesis 1 states that participants will reach good end state at varying lengths of CPT treatment, and they may be characterized into early, standard, late, or nonresponders based on the length of time needed to reach good end state. Because allowing service members to receive a longer course of treatment, if needed, may improve outcomes, Hypothesis 2 states that, given additional sessions, the total percentage of participants who successfully remit from their PTSD will be greater than those in current studies with the standard 12-session CPT protocol.

A second aim of this study is to identify pretreatment factors that account for individual differences in response to treatment for PTSD and to examine predictors of length of treatment needed to achieve treatment success. These predictors include personal factors such as demographics, trauma history, level of combat exposure and other military factors, symptom severity, comorbidities, and personality factors such as internalizing/externalizing traits. Additionally, neuropsychological variables such as cognitive flexibility and inhibition and biological markers such as salivary cortisol and brain-derived neurotrophic factor (BDNF) will be included as potential predictors of treatment response. Hypothesis 3 states that these individual characteristics will predict length of treatment needed to achieve good PTSD end state and ultimately treatment success. Specifically, those who have more problems with externalizing or internalizing symptoms, less cognitive flexibility, more problems with cognitive inhibition, and abnormal regulation of peripheral BDNF and cortisol levels will need a longer course of therapy.

Additionally, because successful treatment of PTSD involves more than remission of PTSD symptoms, a final research objective is to examine secondary outcomes (e.g., work functioning, social/family functioning, aggression, health-risk behaviors) of a varied-length CPT treatment. Hypothesis 4 states that variables such as military factors, trauma history, personality characteristics, and cognitive flexibility/inhibition will predict length of treatment and treatment success on secondary outcomes including work adjustment, aggression, social/family functioning, and health-risk behaviors.

2. Materials and methods

2.1. Participants

Participants are 130 active duty U.S. military personnel age 18 or older seeking treatment for PTSD at the Fort Hood military base after deployments to or near Iraq or Afghanistan. All participants are required to have experienced a Criterion A traumatic event as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* [11] that occurred during military deployment. However, the diagnosis of PTSD may be based on another, worse Criterion A event at any time in their lives. Additional inclusion criteria include diagnosis of PTSD as determined by the Clinician-Administered Posttraumatic Stress Scale for the *DSM-5* (CAPS-5) and the ability to speak and read English.

Exclusion criteria are as minimal as possible in order to increase generalizability of the results. They include: current suicide or homicide risk meriting immediate crisis intervention; active psychosis; and moderate to severe brain damage (as determined by the inability to comprehend the baseline screening questionnaires). Other comorbid conditions (e.g., substance abuse, personality disorders) are not reasons for exclusion. To increase the likelihood that participants will remain in the area long enough to complete the treatment and to improve our ability to track them for follow-up assessments, additional exclusion criteria include the following: local availability of fewer than 5 months; pending Medical Board decision to separate from service; and undergoing an Army chapter, as these may affect the individual's motivation for successful treatment, may result in restricted access to the military installation to attend appointments, and may increase the likelihood of relocation.

2.2. Study design

This is a prospective within-subjects clinical trial designed to determine how much CPT treatment is needed in an active duty military sample with PTSD to reach good end state and to determine predictors of treatment response. All consented participants who meet the inclusion criteria are offered CPT immediately. Following a baseline assessment, participants meet with their therapist for an initial session to establish the index trauma on which to focus in treatment. Participants then receive individual, 50-min CPT sessions twice a week. Participants continue treatment until good end state is established (process described below) or 24 sessions are completed. Participants are required to complete treatment within 18 weeks. Once the participant completes the final therapy session, he/she will then return for follow-up assessments at 1 month and 3 months posttreatment.

2.3. Study procedures

The study is affiliated with the South Texas Research Organizational Network Guiding Studies on Trauma and Resilience (STRONG STAR), a multi-institutional and multi-disciplinary research consortium of investigators based at The University of Texas Health Science Center at San Antonio and focused on the diagnosis, treatment, and epidemiology of combat-related PTSD and co-morbid conditions. This study leverages the STRONG STAR infrastructure in several ways. First, the study is using the common data elements of STRONG STAR and its partnering network, the Consortium to Alleviate PTSD [12]. This will not only help answer the research questions posed in this study, but it also will allow the characteristics of our study sample to be compared to the characteristics of other STRONG STAR studies to ascertain the generalizability of our findings to the larger population of service members with PTSD. This study is employing therapists and independent evaluators trained as part of the consortium and is using the monitoring and quality assurance procedures established for the consortium studies to ensure the fidelity of therapy and independent evaluations in the proposed study. Additionally, the study is overseen by the Data Safety and Monitoring Board (DSMB) established to ensure the appropriate clinical safety monitoring of study subjects participating in the clinical trials conducted by the consortium. In summary, this study is taking full advantage of the structures and processes in place through the STRONG STAR Consortium for a fraction of the expense of setting up such infrastructure de novo.

Recruitment and Screening. The study was reviewed and approved by Institutional Review Boards at The University of Texas Health Science Center at San Antonio (UTHSCSA), VA Boston Healthcare System, and Duke University Medical School. The Carl R. Darnall Army Medical Center (CRDAMC) at Fort Hood deferred its review to the UTHSCSA IRB. The U.S. Army Medical Research and Materiel Command Human Research Protection Office also reviewed and approved the study. Participants are recruited through direct referrals from health care providers at Fort Hood using the CRDAMC electronic medical system. Participants also may self-refer in response to recruitment flyers and pamphlets distributed to health care providers and posted in locations on Fort Hood frequented by service members. Research staff field incoming phone calls and walk-ins and discuss the study treatment and eligibility requirements with the interested person. If a potential participant meets basic eligibility criteria, he or she is consented into the study and completes the baseline assessment.

Assessment Procedures and Measures. All diagnostic clinical interviews are conducted by a masters- or doctoral-level independent evaluator (IE). IEs participate in four stages of training: relevant readings, didactic instruction with an expert in the field, mock interviews, and co-rating exercises with previously taped assessments. After the completion of training, IEs engage in weekly calibration exercises throughout the study to ensure that they continue to meet the high-quality standards of the consortium.

The assessment measures consist of a core battery that has been used in STRONG STAR Consortium studies to fully assess and appreciate complex symptomatology in this patient population [12] plus a number of study-specific measures.

Clinician Administered PTSD Scale for the DSM-5 (CAPS-5). The primary outcome is PTSD symptomatology as assessed by the CAPS-5 [13], a semi-structured interview that assesses PTSD symptom severity and diagnosis. Symptoms are rated on a scale from 0 (*absent*) to 4 (*extreme/incapacitating*). A total symptom severity score is calculated as the sum of the 20 symptom items, with a range of 0–80. The CAPS-5 is administered at baseline and at 1 month and 3 months following treatment.

PTSD Checklist for DSM-5 (PCL-5). Self-reported PTSD symptoms are assessed using the PCL-5 [14,] at baseline, at the follow-up assessments, and every two sessions during treatment. The PCL-5 is a 20-item self-report measure designed to assess PTSD symptoms as defined by the *DSM-5,* based on the original PCL created for *DSM-IV* [15]. Scoring is based on how much the patient has been bothered by the symptoms in the past month (or weekly during treatment) on a scale from 0 (*not at all*) to 4 (*extremely*). Several studies have reported the psychometric characteristics of the PCL-5 in veteran [16] and active duty military [17] samples.

Additional study outcomes and potential predictors of interest are organized into the following areas: (1) history and personality, (2) deployment stress, adversity, and trauma, (3) psychological symptoms, (4) cognitive flexibility and inhibition, (5) functional impairment

(alcohol use, aggression, health, sleep, etc.), (6) other key mediators and moderators, and (7) biomarkers. The full assessment battery, including diagnostic assessments and secondary measures, is administered prior to treatment, and 1 month and 3 months after the final therapy session. Participants also complete several self-report measures weekly during treatment. The measures and schedule of assessments are listed in Table 1.

Neurocognitive Assessments. The participants complete a neuropsychological test battery at baseline and 1 month posttreatment. The battery is estimated to take 1.5 h, depending on individual participant performance. All cognitive testing appointments are scheduled at the

same time, at 9 A.M., to control for any circadian rhythm effects on the biological specimens drawn in coordination with the neurocognitive assessments.

*Cambridge Neuropsychological Test Automated Battery (CANTAB)*The CANTAB is a standardized, computer-based battery of neuropsychological tests administered to subjects using a touch-screen computer. The CANTAB consists of a series of interrelated, computerized, nonverbal tests of memory and learning, working memory and executive function, visual memory, attention and reaction time, semantic/verbal memory, decision making and response control [18]. It has validity established in neurodegenerative diseases, neurosurgical

Table 1
Schedule of assessment measures.

Measure	Baseline	Weekly During Treatment	1-Month Follow-Up	3-Month Follow-Up
History and Personality				
Head Injury Assessment [52]	X		X	X
Self-Injurious Thoughts and Behaviors Interview [53]	X		X	X
Demographics and Military Service Characteristics	X		X	X
Health Interview (Pre- & Post-Treatment)	X		X	X
Internalizing Scale: Mood and Anxiety Symptom Questionnaire (MASQ-Short) [54]	X		X	X
Deployment Stress, Adversity, and Trauma				
Deployment Risk and Resilience Inventory (DDRI-II) Combat Experience, Aftermath of Battle, Deployment Environment & Relationships during Deployment Sub-Scales [55]	X		X	X
Life Events Checklist (LEC) [56]	X		X	X
PERI Life Events Scale [57]	X		X	X
Psychological Symptoms				
Patient Health Questionnaire-9 (PHQ-9) [58]	X	X	X	X
Depressive Symptoms Index-Suicidality Subscale (DSI-SS) [59]	X	X	X	X
Clinician Administered PTSD Scale for *DSM-5* (CAPS-5) [13]	X		X	X
PTSD Check List for *DSM-5* (PCL-5) [15]	X	X	X	X
State-Trait Anger Expression Inventory-2 (STAXI-2) [60]	X		X	X
Generalized Anxiety Disorder Screener (GAD-7) [61]	X		X	X
Cognitive Flexibility/Inhibition				
Delis-Kaplan Executive Function System (D-KEFS) [21]	X		X	X
Cambridge Neuropsychological Test Automated Battery (CANTAB) [62]	X		X	X
Attentional Network Task (ANT) [22]	X		X	X
Implicit Association Test (IAT) [63]	X		X	X
Functional Impairment (alcohol use, aggression, health, sleep)				
Alcohol Use Disorders Identification Test (AUDIT) [64]	X			
Quick Drinking Screen Self-Report Version [65]	X		X	X
Revised Conflict Tactics Scale (CTS-2) Physical Assault & Psychological Aggression Subscales [66]	X		X	X
Patient Health Questionnaire (PHQ-15) [67]	X		X	X
Veterans RAND 12-Item Health Survey (VR-12) (Functional Impact) [31]	X		X	X
West Haven Yale Multidimensional Pain Inventory (WHYMPI) [68]	X		X	X
The Inventory of Psychosocial Functioning (IPF) [69]	X		X	X
Snoring, Tired, Observed, Blood Pressure (STOP) Sleep Apnea Screen [70]	X			
Patient Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance and Sleep-Related Impairment Short Forms [71]	X		X	X
Insomnia Severity Index (ISI) [72]	X		X	X
Other Key Mediators and Moderators				
Trauma-Related Guilt Inventory (TRGI) [73]	X	X	X	X
Inventory of Complicated Grief (ICG) [74]		X	X	X
Childhood Trauma Questionnaire (CTQ) [75]		X		
DRRI-2-Support from Family and Friends Subscale [55]	X			
Post-Deployment Support, Unit Social Support [55]	X		X	X
University of Rhode Island Change Assessment Scale (URICA-T) Trauma Version [76]	X	X		
Readiness Ruler [77]	X	X		
Working Alliance Inventory (WAI) [78]		X		
Homework Compliance		X		
Resting Heart Rate and Blood Pressure	X		X	X
Salivary Cortisol	X		X	X
Blood Sample for Brain-Derived Neurotrophic Factor (BDNF)	X		X	X

cases, psychiatric disorders and acquired pathology [18–20]. The battery contains measures of attention, information processing speed, executive function memory, decision making, cognitive flexibility and impulsivity. A detailed description is at http://camcog.com/cantab-tests.asp.

Delis-Kaplan Executive Function System (D-KEFS). The D-KEFS [21] is a set of standardized tests for comprehensively assessing higher-level cognitive functions, referred to as executive functions, in both children and adults (aged 8 to 89). In this study, three of the D-KEFS tests are being administered. The D-KEFS Sorting Test is similar to the Wisconsin Card Sorting Test. The test measures a number of processes of executive function, including problem-solving, inhibition, and flexibility of thinking and behavior. Alternate forms allow for repeated measures to assess changes in these constructs following treatment. The D-KEFS Color-Word Interference Test is similar to the Stroop Interference Test. This test measures the ability to inhibit an overlearned verbal response to generate a conflicting response. Additionally, an inhibition/switching condition evaluates both inhibition and cognitive flexibility, and it is used to evaluate ability to inhibit perseverative verbal responses. This test is repeatable to assess changes following treatment.

Attentional Network Task (ANT). The ANT [22] is a neurocognitive computerized measure designed to evaluate alerting, orienting, and executive functioning in visual processing. Efficiency of the three attentional networks is assessed by measuring how response times are influenced by alerting cues, spatial cues, and flankers. Research using the ANT has shown specific deficits in executive functioning among participants meeting criteria for PTSD relative to participants with similar trauma histories but no PTSD and those with a minimal history of trauma [23]. The two other attentional variables have not been shown to be sensitive to PTSD; therefore, they are serving as control conditions to demonstrate that there is a relationship between specific cognitive processes and PTSD treatment/outcome as opposed to a more general effect on all aspects of attention.

Biological Specimens (salivary cortisol and plasma BDNF). A series of six saliva samples are obtained prior to and following cognitive testing conducted at baseline and 1 month following treatment. Participants are provided with saliva cryovials prior to the appointment and instructed to collect saliva samples by passive drool at three time points prior to their appointment: (1) before bedtime the night before, (2) at wake-up, and (3) 30 min after waking on the day of the appointment. Upon arrival and following a 10-min check-in procedure, saliva samples are collected followed by blood collection (10 ml) by venipuncture. Saliva and blood samples are also collected immediately and 30 min after cognitive testing.

Treatment Description. CPT [24,25] is a highly structured, manualized protocol in which clients learn the skills of recognizing and challenging dysfunctional cognitions, first about their worst traumatic event and then to the meaning of the traumatic event in shaping current beliefs about self and others. In CPT, there are practice assignments, typically progressive worksheets to complete each day between sessions. The following content is discussed in the sessions: *Session 1:* The initial session of CPT is psycho-educational; symptoms of PTSD are explained within a cognitive and information-processing theory framework. At the conclusion of this session, patients are asked to write an impact statement about the meaning of the traumatic event, as well as beliefs about why the event happened and the impact of the event on beliefs related to areas that are often impacted by trauma (i.e., safety, power/control, trust, esteem, and intimacy). *Session 2:* In Session 2, the impact statement is read and discussed with a focus on identifying problematic beliefs and cognitions (called "stuck points") which are noted on a Stuck Point Log. The therapist introduces the Activating Event – Belief – Consequence (A-B-C) Worksheet with an explanation of the relationship between events, thoughts and subsequent emotions. Patients are then taught to identify the connection between events, thoughts, and feelings and asked to practice this skill for homework.

Sessions 3–4: Sessions 3 and 4 include a review of the self-monitoring homework and a discussion of stuck points. Socratic questioning is first used to identify dysfunctional thoughts about the worst traumatic event (index event) such as erroneous self-blame. Participants are then re-assigned daily A-B-C Worksheets about the index event. In Session 4, participants are given the Challenging Questions Worksheet, which examines single beliefs related to the trauma through a series of questions. *Sessions 5–6:* In Session 5, the Challenging Questions Worksheet is reviewed and the Patterns of Problematic Thinking Worksheet is introduced. Session 6 focuses on the identification of patterns of problematic thinking through both homework review and the introduction of the Challenging Beliefs Worksheet, which incorporates all of the other worksheets and adds the generation of a more balanced factual alternative thought to practice. Participants are asked to use the worksheets daily with everyday events and to challenge trauma-related self-blame cognitions. *Sessions 7–12:* In Sessions 7–12, over-generalized beliefs are challenged in the five areas of safety, trust, control, esteem, and intimacy as they relate to self and others. Treatment gains are consolidated in the final sessions. *Sessions 12–24 (if needed):* Participants continue to challenge remaining stuck points using additional Challenging Beliefs Worksheets for the remainder of the treatment. In the event that significant participant crises occur during the course of treatment, up to two sessions are permitted to focus on the crisis situation. Following procedures used in other studies of CPT [8,10,24,26] when a participant experiences a significant stressor that may interfere with treatment, the participant and therapist may discuss postponing CPT content and instead focus the session on addressing the current stressor. CPT is then resumed in the following session.

Determination of Good End State. Participants complete the PCL-5 every two sessions to assess for good end state, which is defined as a score of ≤19 on the PCL-5 and agreement by the patient and therapist that the patient is finished with therapy. Good end-state score on the PCL-5 (≤19) was suggested by Weathers and Schnurr (personal communication, November 26, 2014) and has been used to define stable remission in a large multi-site ongoing trial of CPT in the Department of Veterans Affairs (VA) [26]. If the participant has met the PCL-5 cutoff, the therapist and patient discuss whether the patient is finished with therapy or if he/she should continue. If the patient and therapist decide to stop treatment at that time, the patient returns in 1 week for a final session. If the patient still meets good end state (PCL ≤ 19) at this session, it is the final session. He or she will review the final impact statement and receive and review any CPT materials not covered in the treatment received. If the participant's PCL score no longer meets good end state at this session, he/she continues with treatment until the PCL score returns to good end state and the therapist and participant agree to end treatment. The assessment of progress continues every two sessions. Participants can receive up to 24 sessions, which is twice the length of the usual protocol. In these additional sessions, the patients will continue practicing skills using protocol handouts, the stuck point log, and Socratic dialogue learned in the 12-session protocol until good end state is achieved. No new worksheets or therapy techniques will be added.

Training and Supervision of Therapists. The therapists are trained to conduct the therapy by the last author or another qualified CPT trainer following established procedures used by the STRONG STAR Consortium and in other studies [8,24]. Video recordings of treatment sessions are reviewed by designated CPT supervisors/consultants, and all therapists are required to meet therapy fidelity requirements prior to seeing consented study cases. During the data-collection phase, therapists continue to receive weekly supervision or consultation on their cases by project staff. They have local back-up as well as case consultation with the overall study principal investigators on an ongoing basis as needed. All therapists participate in a weekly CPT therapist teleconference with the CPT consultants to review all new and ongoing treatment cases.

Fidelity Monitoring. Treatment adherence and competence is

determined by independent raters who are not otherwise involved in the project. The raters have served on prior CPT studies as fidelity raters. The raters determine adherence to CPT and competence in delivering the therapy by reviewing videotapes of treatment sessions and completing standardized rating forms developed and used in prior studies of CPT [8,24]. Ten percent of sessions are randomly selected for rating by a computer program implemented by a staff member not otherwise associated with treatment, and 20% of the rated sessions are rated by both raters for determination of inter-rater reliabilities (kappas).

2.4. Data analytic strategy

Statistical Analysis Plan. All participants will be included in analyses (intention to treat) regardless of the amount of treatment they receive. All participants are asked to complete assessments 1 month and 3 months after treatment ends regardless of the outcome. Our primary analysis plan is largely based on the approach used by Galovski [10,27]. Participants will be classified into one of four outcome groups on the basis of end-state PCL-5 scores and the length of treatment: (1) Early Responders: those who reach good end state with fewer than 12 sessions; (2) Standard Responders: those who reach good end state in exactly 12 sessions; (3) Late Responders: those who reach good end state with 13 sessions or more; (4) Non-Responders: those who complete 24 sessions or reach the 18-week treatment window without reaching good end-state scores. Participants who leave treatment prior to session 24 without reaching good end state will be considered dropouts. However, another consideration is that the nature of active duty military service may require some participants to leave treatment for reasons out of their own control (e.g., deployment or permanent change of duty location). Participants who leave the study under such circumstances will be defined as "pull-outs" rather than "drop-outs," and may be excluded from some analyses because their true end state is not known.

We will report the proportions classified into each of these outcome categories and descriptive statistics such as the average, range and distributions of the number of sessions completed in each subgroup with 95% confidence limits. The outcome groups will then be compared on baseline descriptive, service history, and clinical characteristics to identify prognostic variables using conventional methods such as analysis of variance and chi-square. The trajectories of symptoms and secondary outcome measures over time in each of these subgroups will be described and compared with linear and generalized mixed effects regression models with repeated measures, and the differences between subgroups characterized in terms of standardized effect sizes. As Galovski and colleagues [10] noted, these outcome subgroups are defined by the degree and timing of symptom improvement, so inferential statistical tests of those measures are tautological. However, such comparisons are valid for the secondary outcome measures, which may not be highly correlated with primary symptom outcomes and are not used to make the outcome subgroup classifications.

Predictors of time to recovery will be analyzed using survival analysis methods. The Kaplan-Meier (product limit) survival curve estimates the proportions of participants reaching good end state at each session and gives cumulative estimates of proportions responding over time. Nobler et al. [28] compared four alternative data analysis methods for the study of time to recovery and concluded that survival analysis was most powerful. Proportional hazard survival regression will be used to examine baseline characteristics as predictors of speed of recovery [29]. We will also explore the value of analyzing dropout and recovery as competing risks, treating dropout and recovery as two clinically meaningful events [30].

We will also use growth mixture modeling, or Latent Transition Analysis (LTA) to define outcome groups. LTA does not depend on arbitrary cutoffs. LTA is a data-driven type of cluster analysis that assumes that the participants are drawn from a heterogeneous population comprised of underlying unmeasured groups of individuals who share similar trajectories over time. Subgroups are defined using growth model parameters such as intercepts and linear or nonlinear trends. As implemented in SAS PROC TRAJ [31], for example, the user specifies the hypothesized number of latent groups, the growth function that describes the trajectory (up to a third degree polynomial), and the error distribution (e.g., normal, Poisson, ZIP, logit). Fitting multiple models with different specifications permits selection of a "best" model based on the Bayesian Information Criterion. LTA makes no *a priori* assumptions about the patterns of symptoms over time. Information criteria are used to guide the decision as to how many subgroups exist. Individual participants are assigned to the most likely subgroup on the basis of estimates of probabilities of subgroup membership, which then can be compared using conventional analysis methods.

Finally, we will examine differences between outcome subgroups on baseline characteristics using recursive partitioning or classification and regression trees (CART) [32]. CART is an empirical, data-driven, computer-intensive methodology that exhaustively searches a set of variables to build (or "grow") a decision tree for classification of patients. CART yields a simple prediction algorithm that is intuitive and easily understood and can be applied without complex computation. It can discover interactions among predictors in a way that is not possible with conventional parametric regression models. Accuracy of prediction in CART is evaluated with cross-validation, holding out some participants in the tree-building process and then using the omitted cases to evaluate the accuracy of prediction.

Biomarker Analysis. BDNF levels in plasma will be analyzed using the Milliplex® Map Human Magnetic Bead Panel 3 immunoassay for BDNF in saliva and blood in duplicates as per manufacturer's protocol (EMD Millipore, MI). The samples will be analyzed using Luminex Flex Map3D (Luminex Corporation, Austin, TX). BDNF (in pg/ml) will be calculated in MFI on the basis of the standard curve. Free cortisol levels in saliva will be determined in triplicate using the Salimetrics® Cortisol Enzyme Immunoassay Kit, a competitive immunoassay specifically designed and validated for the quantitative measurement of salivary cortisol (Salimetrics LLC, State College PA, USA).

Genomic DNA will be isolated from whole blood using a Tiangen DNA isolation kit. Genotyping of the BDNF Val66Met single nucleotide polymorphism (SNP) will be carried out using the TaqMan SNP Genotyping Assay on ABI PRISM 7900 sequence detection instrument and SDS 2.0 software. For quality control, all genotypes will be determined blindly in the genotyping processes. The genotyping assays will be repeated type to make sure that the results are concordant structure, and the ability to perform between- and within-groups contrasts both and across assessments. The Val66Met SNP will be analyzed using the Hardy-Weinberg equilibrium testing and allele and genotype frequency analysis. The association of Val66Met genotypes and the selected cognitive domains will be compared between the patient with Met Allele (Val/Met + Met/Met) and those without Met allele (Val/Val).

Sample size. For an analysis of variance comparing four groups of roughly equal size, power with total $N = 130$ is 0.80 if Cohen's $f = 0.30$ [33], slightly larger than his convention for a "medium" effect. Survival regression analysis has power = .80 to detect a hazard ratio of 1.75, representing a different in recovery rates of about 15–20%.

The bulk of potentially consequential missing data occurs when participants drop out and data are missing from that point on. Typically, more complex analyses of missing data patterns are not needed. Individual forms or entire assessments are occasionally missed, but that is generally reasonably attributed to extraneous factors (e.g., illness, child care). Dropout is one of the outcome categories into which participants may be classified, and examination of characteristics associated with dropout including baseline descriptive and clinical characteristics and early outcome trajectories prior to dropout is a primary aim of the study. With respect to missing data, the likelihood-based methods of statistical analysis such as those implemented in the

mixed effects regression modules in the popular statistical libraries yield valid estimates given the commonly made assumption that data are missing at random.

3. Discussion

Given the unique nature of combat-related PTSD in active duty military and returning veterans, there is an urgent need to identify effective treatments for this condition in this population. Current and previous versions of the *VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder* [34] have included CPT as one of the first-line recommended treatments for PTSD, and numerous clinical trials have demonstrated its efficacy in a range of populations. Although CPT is shown to be efficacious in active duty and veterans [5,8,24,35], the effects have been smaller than for civilian samples, with 49%–67% experiencing a meaningful symptom reduction and one third losing the diagnosis of PTSD [9]. However, a recent meta-analysis indicates that CPT has the highest effect size (mean ES = 1.33) of existing evidence-based treatments for PTSD in military personnel and veterans [36]. This suggests that there is benefit to treating military personnel with PTSD using CPT, while it remains important to continue seeking methods to improve its efficacy. Tailoring treatment using a variable-length protocol could allow patients previously deemed "refractory" to reach good end state by allowing more sessions to be added to the standard treatment protocol. Conversely, patients who are rapid responders may end treatment prior to receiving 12 sessions and return to their duties and lives more quickly.

This study is the first to examine a variable-length treatment for PTSD in an active duty military sample. We seek to establish a method for modifying standard CPT in this population, specifically by formalizing the assessment of good end state and determining the appropriate criteria for stopping treatment early or continuing treatment longer. Importantly, we also will examine predictors of treatment outcome. Establishing factors that indicate whether a service member is likely to respond to CPT—and whether he or she might be an early responder or may require additional sessions to achieve full benefit—could assist in treatment planning for this population.

Previous studies that have examined predictors of treatment response in PTSD have typically examined patient demographic variables [37,38]. This study is unique in that it includes an examination of potentially important but understudied factors that may contribute to treatment outcome and length of time to achieve good PTSD end state. Recent studies suggest that the internalizing/externalizing model of personality and comorbidity may be relevant to understanding patterns of posttraumatic psychopathology and their links to treatment outcome [39–42]. Based on this research and theory, we hypothesize that individual differences in internalizing and externalizing psychopathology will be associated with poorer treatment outcome, but for different reasons. Internalizing (which is also associated with the tendency to ruminate about past traumas, failure experiences, etc.) is expected to predict deficits in cognitive flexibility and inability to inhibit, which in turn will be associated with longer or poorer response to treatments that require the ability to change one's thinking about a past traumatic experience. In contrast, higher levels of externalizing will be associated with deficits in cognitive flexibility and inhibition that may lead to impulsivity, aggression, or substance abuse.

Additionally, this study is the first to include neuropsychological predictors of response to CPT. The inclusion of these assessment batteries will allow for the examination of potential mechanisms for change in CPT and can inform which patients could most benefit or may have difficulty with the cognitive focus of the therapy. Over the past two decades, neuropsychological studies of patients diagnosed with PTSD have reported impairments in executive functions, including cognitive flexibility (e.g. Ref. [43]). Cognitive flexibility is the capacity to shift one's train of thought and action according to changing demands of the environment and new information and is a facet of frontally mediated cognitive control/executive functioning abilities [44]. It may also include the ability to inhibit information that is incorrect. In adults, it is a trait-like ability indexed by performance on well-established neuropsychology tests. Changing the meaning of the traumatic experience and abandoning maladaptive trauma-related cognitions in favor of new more adaptive ones are fundamental components of the change process for CPT. The ability to incorporate new information about the traumatic experience and inhibit over-learned cognitive and behavioral responses associated with it may be, at least in part, dependent on the patient's capacity for cognitive flexibility and ability to inhibit dysfunctional thoughts. Specifically, patients who are cognitively inflexible will often perseverate in unproductive lines of reasoning that make them difficult to treat. Accordingly, we hypothesize that pretreatment individual differences in this capacity will predict treatment length and outcome. Evaluating these variables as pretreatment predictors of outcome and length of response to treatment may be an essential first step toward the future development of treatment matching and treatment combination algorithms that would better address the unique needs of individual patients, including those who are refractory in response to treatment-as-usual.

The inclusion of biological measures as predictors of treatment response is also a novel aspect of the study. Although BDNF and salivary cortisol have been implicated in the traumatic stress response and the response to treatment [45–47], to date there are no published trials examining these biomarkers in the context of CPT. PTSD risk is associated with BDNF Vall66Met SNP and BDNF overexpression [47]. Previous studies have also shown a SNP in the Met-66 allele of the BDNF, which results in lower activity-dependent secretion, predicts poor response to exposure therapy in PTSD and impaired fear extinction in healthy controls [45]. The BDNF Val66Met polymorphism moderated the relationship between PTSD and fear extinction learning, such that poorer fear extinction learning was associated with greater PTSD symptom severity (and PTSD diagnostic status) in individuals with the low-expression Met allele [46].On the other hand, Rauch and colleagues [48] reported that increased cortisol response to personal trauma script prior to PTSD therapy and reductions in cognitive symptoms of PTSD were significantly and uniquely related to reductions in the core symptoms of PTSD in Prolonged Exposure (PE) therapy. In another study, they reported that low treatment responders showed greater increases in salivary cortisol output over the course of PE treatment, indicating that increases in hypothalamic-pituitary-adrenal axis reactivity over the course of psychotherapy may be associated with worse treatment response [49].

In addition to examining changes in PTSD and other mental health symptomatology following CPT, this study also seeks to assess improvements in functioning domains beyond psychopathology. Few published studies to date have examined the full range of psychosocial functioning outcomes following PTSD treatment. Several secondary analyses of previous CPT trials have shown improvements in symptoms such as physical health and sleep, and psychosocial functioning in the areas of work, family, and social/leisure activities [50,51]. However, the samples in these studies were comprised of female civilian assault victims. It remains to be seen how psychosocial functioning and physical health outcomes may be affected by CPT in an active duty military sample. Furthermore, health risk behaviors such as substance abuse and aggression also may be important outcomes to examine in this active duty population. No clinical trials to date have reported changes in these behaviors following CPT treatment. The current study includes an extensive battery of secondary measures to assess the effect of variable-length CPT on a wide range of functioning outcomes.

This study challenges the "one-size-fits-all" approach to trauma treatment and attempts to develop a more tailored and personalized approach to achieving positive treatment outcomes for service members suffering with PTSD. Testing a variable-length version of CPT will determine if increasing the length of the treatment will result in a greater

number of service members achieving good end state. It also will also explore if some service members may reach good end state in a shorter amount of time, allowing them to return to duty and resume their lives more quickly. This study seeks to further the knowledge of precision medicine in the field of PTSD treatment by examining potential predictors of CPT treatment response, including neuropsychological and biological factors. Results of this study may help guide treatment matching, first through a greater understanding of which characteristics make someone most likely to benefit from CPT, and second, by illuminating how the course of treatment might be shortened or lengthened to optimize outcomes for particular patients.

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None to report.

Disclaimer

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