Protocol Summary

Title:	Evaluating The Efficacy of Combined Cognitive Processing Therapy and Stellate Ganglion Blocks for PTSD: A Randomized Controlled Trial
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Project Overview

Posttraumatic stress disorder (PTSD) affects approximately 23% of veterans and is associated with numerous negative mental health outcomes, including decreased quality of life, substantial impairments in work, home, and social functioning, increased risk of suicide, and poorer long-term physical health. Despite the existence of evidence-based treatments for PTSD, research has demonstrated that 14-50% of those receiving these gold-standard PTSD treatments either do not respond or exhibit a diminished treatment response. Consequently, there is a clear need to explore ways to improve existing treatment outcomes. Given the strong evidence supporting existing first-line treatments, such as Cognitive Processing Therapy (CPT), it is likely that augmenting these treatments with novel therapeutics that have shown promise in the treatment of other conditions can further enhance outcomes beyond each treatment alone. One such therapeutic is Stellate Ganglion Block (SGB), which has been safely used in the treatment of chronic pain and other conditions. SGB has recently been shown to be effective at reducing PTSD symptoms.

The proposed project will systematically test whether combining CPT with SGB produces greater PTSD symptom reductions and functional improvements in the short- and longer-term up to 6-months follow-up compared to CPT (+Placebo) or SGB (+Daily Monitoring) alone.

Scientific Review

First-Line PTSD Treatments

PTSD is a debilitating mental health condition that impacts approximately 23% of Veterans. Between 2001-2017, the average incidence rate of PTSD in the U.S. military was 7.88 per 1000 service members, with a peak incident rate of 12.94. Moreover, PTSD is associated with high rates of comorbidity and high degrees of functional impairment, more so than any other mental health disorder. Untreated PTSD has been shown to lead to substantial impairments in work, home, and social functioning, increased risk of suicide, and poorer long-term physical health outcomes.

The Veterans Administration and Department of Defense (VA/DoD) Clinical Practice Guidelines recommend CPT, among other interventions, as a first-line psychotherapeutic intervention for the treatment of PTSD. CPT can produce large PTSD symptom reductions. These PTSD symptom reductions are lasting and can be maintained for 10 years or more. CPT has been successfully used with a wide range of populations, including service members and Veterans. The primary mechanism of action in CPT is hypothesized to be a reduction in negative trauma-related cognition about oneself, others, and the world.

While CPT is traditionally delivered weekly over 12 sessions, our research group and others have recently demonstrated that CPT can be successfully administered in as little as a single week. In our recently completed clinical trial we also demonstrated that 1-week massed CPT can be effectively delivered via telehealth. Completion rates for 1-week massed CPT were extremely high with 96% of participants completing the entire course of treatment, suggesting excellent feasibility. The results from the 1-week massed CPT trial suggest that 87% of study participants experienced clinically significant PTSD severity changes after the single week, with

the majority of participants experiencing clinically meaningful improvement in PTSD symptoms after the fourth session (i.e., after two days of treatment). Symptom reductions achieved throughout 1-week massed CPT were maintained at the 3-month follow-up. Importantly, participants found the extremely brief treatment helpful and reported that it helped them remain focused on the treatment and acquire the necessary skills to effectively manage their PTSD symptoms. We have also shown that the massed/daily delivery of CPT is feasible and effective at reducing PTSD symptom severity with gains maintained for at least 12 months.

Non-Response to First-Line PTSD Treatments

Despite the demonstrated effectiveness of first-line PTSD treatments, not all individuals who receive these treatments show a favorable response. Research has demonstrated that 14-50% of those receiving gold-standard first-line PTSD treatments either do not respond or exhibit a diminished treatment response. Other studies have suggested that approximately two-thirds of treatment completers continue to meet PTSD diagnostic criteria and therefore continue to be at risk for reduced work, home, and social functioning. Moreover, meta-analyses suggest that service members and Veterans are less responsive to first-line PTSD treatments compared to civilians. Based on these data, it can be expected that many service members and Veterans will retain their PTSD diagnosis following an initial course of a first-line PTSD treatment, highlighting the need to identify better treatment options.

Stellate Ganglion Block May be a Promising Treatment Option

The stellate ganglion (SG) is a collection of sympathetic nerves found at the level of the sixth and seventh cervical ganglion. The SG forms as a result of the fusion of the inferior cervical and first thoracic sympathetic ganglions. Clinical blockade of the SG is useful for a wide variety of diagnostic and therapeutic indications and is becoming a well-researched and well-established treatment for a variety of physical health concerns, including chronic pain. SGB has recently been shown to also be effective for reducing PTSD symptom severity. SGB is a treatment that involves an injection of local anesthetic around the stellate ganglion (located at the base of the neck) to block its transmission of pain signals.

A recent sham-controlled randomized clinical trial suggested that SGB produces significantly greater PTSD symptom reductions compared to saline injections. Similarly, case series studies and reviews support the safety and effectiveness of SGB in reducing PTSD symptoms. Studies have indicated that SGB's impact can last over time, although there is a clear need for studies that examine treatment effects for more than three months. SGB has been determined to be safe and is particularly well-received by military populations.

Research suggests that SGB may be particularly effective at reducing hyperarousal symptoms. This is particularly important because first-line psychotherapies have been shown to have a limited impact on hyperarousal symptoms. Combining CPT and SGB may therefore enhance the efficacy compared to each treatment used as a standalone intervention and provide a relief with common residual symptoms, such as irritability or angry outbursts, difficulty concentrating, and sleep disturbance.

Individuals with PTSD most notably reported significant enhancements in the initial week following the SGB procedure. This immediate post-procedural period might serve as an opportune

time to initiate trauma-focused psychotherapy. The initial symptom alleviation resulting from SGB could enhance individuals' receptivity to interventions like CPT. This heightened engagement, stemming from symptom reduction, might further catalyze cognitive and behavioral shifts in individuals. Such transformations could not only amplify the therapeutic outcomes beyond those achieved by standalone treatments but also ensure the longevity of these benefits.

Complementary Treatment Mechanisms

CPT and SGB are hypothesized to operate via distinct mechanisms that may complement one another in the treatment of PTSD. CPT is a primarily cognitive intervention that teaches individuals to identify negative posttrauma cognitions about the cause of the traumatic event (i.e., "It was my fault," "If only I had done something differently the event wouldn't have happened," "If people had done their jobs, everyone would have survived"), as well as overgeneralized beliefs stemming from the trauma about themselves, others, and the world (i.e., "The world is unsafe," "I can't trust anyone," "I am damaged") and identify related emotions. These distorted beliefs are thought to fuel trauma-related symptoms and functional impairment.

The mechanism by which SGB exerts therapeutic effects in PTSD, on the other hand, is postulated to primarily revolve around the modulation of the sympathetic nervous system. The SG, located at the juncture of the cervical and upper thoracic vertebrae, serves as a critical nexus in sympathetic innervation, influencing various physiological functions. Upon administering SGB, a local anesthetic is delivered around the SG leading to an effective interruption of sympathetic outflow. This intervention is theorized to induce a subsequent reduction in overall sympathetic tone, diminishing the heightened state of arousal characteristic of PTSD. Beyond simple sympathetic downregulation, emerging research highlights potential neurochemical alterations secondary to SGB. Particularly, there may be modifications in neurotransmitter dynamics, with norepinephrine—a key sympathetic neurotransmitter that's often dysregulated in PTSD—being of primary interest. By modulating sympathetic activity, *SGB might catalyze a more adaptive form of neural plasticity, enabling neural circuits to reorient towards a more normalized state associated with fewer PTSD symptoms*.

The Importance of Testing Combined CPT and SGB

Taken together, evidence points to the ability of CPT and SGB to reduce the severity of PTSD symptoms in short periods via two distinct psychological (i.e., changes in trauma-related cognitions) and biological (i.e., sympathetic/parasympathetic balance) mechanisms. However, no studies to date have systematically examined whether combining these two interventions produces larger effects than each intervention alone. Consequently, there is a critical need to examine CPT and SGB in combination to determine whether this could have a positive impact on overall PTSD treatment response rates. Since both treatments are widely available, finding support for the hypothesis that CPT+SGB produces stronger outcomes than each treatment alone could result in rapid dissemination which may help a greater number of service members and Veterans experience larger improvements compared to each treatment alone as is the case in current practice.

Measuring Physical Health Improvements via Heart Rate Variability

SGB is theorized to exert a direct influence on the autonomic nervous system, predominantly through tempering the sympathetic nervous system's activity. The equilibrium between the sympathetic and parasympathetic arms of the autonomic nervous system is represented by a metric known as heart rate variability (HRV. HRV refers to the variation in time intervals between consecutive heartbeats. In essence, a higher HRV signifies greater adaptability and resilience of the heart, indicative of a harmonious balance between sympathetic and parasympathetic inputs. Numerous studies have unequivocally associated enhanced HRV with robust cardiovascular health, augmented physical stamina, and optimal physiological functioning. Moreover, lower HRV has been correlated with an array of adverse health outcomes, including increased susceptibility to cardiovascular disease and reduced life expectancy.

Despite the established connection between HRV and overall health as well as PTSD, there remains a paucity of research dissecting the direct influence of evidence-based psychotherapies (EBPs) for PTSD on HRV or broader physical health parameters. Evidence-based psychotherapies such as CPT have been predominantly investigated concerning their therapeutic efficacy on psychological parameters, with less emphasis on physiological outcomes. Therefore, it is paramount to discern if such psychotherapies can directly ameliorate physical health or if their positive repercussions on health are predominantly mediated by reductions in PTSD symptomatology.

Research Plan

Objectives

To systematically address questions surrounding improving PTSD treatment, the proposed 3-arm randomized controlled clinical trial will directly compare the combination of CPT+SGB vs. CPT (+Placebo) vs. SGB (+daily monitoring) in a total of 180 service members, Veterans, and civilians with PTSD. Short- and longer-term (up to 6-month follow-up) impacts of the respective interventions on both PTSD symptoms and functioning will also be assessed.

Objective 1

Determine the efficacy of combining CPT and SGB for reducing PTSD symptoms and improving functioning. H1a: Participants who receive CPT+SGB will experience greater reductions in PTSD symptoms based on clinician-administered and self-reported PTSD assessments and greater improvements in functioning compared to each intervention alone. H1b: Clinician-administered and self-reported PTSD symptoms will reduce to a greater extent immediately after and 3- and 6-months following treatment for participants assigned to the CPT+SGB condition vs. those who receive CPT (+Placebo) and SGB (+daily monitoring).

Objective 2

Probe changes in negative posttrauma cognitions and sympathetic/parasympathetic balance as potential complementary treatment mechanisms. H2a: Negative posttrauma cognitions will improve over the course of CPT+SGB and CPT and improve to a greater extent than for individuals who receive SGB. H2b: Greater reduction in the sympathetic/parasympathetic balance, assessed via heart rate variability (HRV), will be experienced by individuals assigned to the CPT+SGB and SGB conditions compared to individuals who receive CPT. H2c: Changed in negative posttrauma

cognitions and sympathetic/parasympathetic balance will predict short- and longer-term (6-month) PTSD symptom reductions and functional improvement.

Secondary Objectives

The study is also designed to examine the effects of each treatment on physical well-being, as assessed via heart rate variability (HRV), which has been closely linked to long-term physical health.

Target Population and Sample Size

We will consent and enroll a total of approximately 180 service members, veterans, and civilians with PTSD. Based on our prior trials with this population, we anticipate that ~25-50% of potential participants will not meet inclusion criteria or will not start treatment. Thus, we plan to recruit 270 individuals to have a final sample of 180 service members, veterans, and civilians who start treatment. We will purposely oversample for veterans and service members with the goal of recruiting approximately n = 90 veterans and/or service members and approximately n = 90 civilians for the final sample.

Study Timelines

For participants, this study is expected to take 7.5 months to complete. Based on our experiences with a recent SGB pilot study, we anticipate the screening, intake, and treatment scheduling process to take approximately 1 month to complete. The treatment process is expected to take two weeks to complete. The remaining six month duration of the study will be spent completing follow-ups, which will occur up to six months following participants' second SGB/placebo saline injection.

Inclusion and Exclusion Criteria

Individuals are *eligible* for the current study if they:

1. Are 18 years or older
2. Are fluent in English
3. Have experienced a Criterion A traumatic event during their lifetime
4. Have a PTSD diagnosis verified via the Clinician Administered PTSD Scale for DSM-5
5. Have not previously received an SGB
6. Have a smartphone that they can use for the entire duration of the study
7. Are willing and able to receive 2 injections (SGB or placebo) 2 weeks apart at the Rush Pain Clinic
8. Are willing and able to participate in daily CPT or Daily Monitoring over the course of one week
9. Are willing and able to complete self-report measures and clinician-rated assessments at multiple time points over the course of the study

Individuals are *excluded* from the current study if:

1. The traumatic event occurred in the past month

2. They are currently suicidal or homicidal (i.e., plan and intent)
3. They have unmanaged psychosis or mania
4. They have not been on a stable dose of psychotropic medication for at least one month by the time of the baseline assessment or are planning to change their medications within 3 months of starting their participation in the study
5. They have completed an evidence-based cognitive behavioral PTSD treatment (e.g., CPT or Prolonged Exposure) in the past 3 months or are currently receiving an evidence-based PTSD treatment
6. They have an intellectual disability or significant cognitive impairment that would prevent them from engaging fully in treatment
7. They are currently on any blood-thinning medications or have a coagulopathy
8. They have any of the following conditions: a recent myocardial infarction, glaucoma, a pre-existing contralateral nerve palsy, severe emphysema, or a cardiac conduction blockade.
9. They are allergic to any of the medications injected (i.e., ropivacaine, lidocaine, propofol)
10. They have an active infection
11. They have a serious or unstable medical illness or instability for which hospitalization may be likely within the next year
12. They have a visual or auditory impairment that would prevent them from fully participating in study activities
13. They are involved with current legal actions related to the traumatic event that is anticipated to be targeted during treatment
14. They have substance dependence that, in the judgment of the Principal Investigator, may require hospitalization if substances were discontinued.
15. Subjects who, at the time of consent, appear to have extenuating life circumstances (e.g., unstable housing, no internet access, etc.) which, in the judgment of the Principal Investigator, could affect the ability to deliver the intervention with fidelity

These inclusion criteria are as broad as possible to allow for the trial to apply to real-world clinical settings. The exclusion criteria were chosen to identify individuals that have certain comorbidities or circumstances that would make engagement in a cognitive-based treatment difficult or potentially interfere with a clinician's ability to deliver the intervention with fidelity. The exclusion criteria chosen would be considered as a part of standard clinical care outside of a research setting for those seeking CPT or SGB treatment for PTSD.

Study Activities

Eligibility Phone Screening

Individuals who are interested in participating in the proposed study will call study staff in response to study recruitment flyers or will be called by the study staff once they have been referred. The eligibility screening will be conducted over the phone. Interested individuals will be asked for their verbal consent to participate in the eligibility screening and then screened to determine potential eligibility. Individuals who meet exclusion criteria during the screening or

virtual baseline visit or who choose not to participate will be referred for other treatment/resources as indicated. Potentially eligible individuals will be sent the electronic consent form.

Informed Consent

Informed consent will be obtained by trained members of the study staff before the baseline assessment. Potential participants will be emailed the electronic consent form via REDCap, a HIPAA-secure platform. Study staff will call and explain the study to the potential participants and answer any questions they have. Potential participants will be encouraged to carefully read the entire consent form and to take their time to consider if they would like to participate. Potential participants can take as much time as they need to decide if they would like to participate and reach out to study staff with any questions they may have. Potential participants will be allowed to discuss the study with others (e.g., an outside treatment provider) if they would like to before consenting.

If at any time reconsent is needed, participants will be sent a new electronic consent form via REDCap and study staff will inform them of any changes that were made.

Virtual Baseline Assessments

Under the supervision of the Principal Investigator, who is a licensed clinical psychologist, trained study staff, with at least a Bachelor's degree and who are not providing the treatment, will conduct structured diagnostic interviews. These interviews are to determine eligibility by confirming a diagnosis of PTSD, as assessed by a gold-standard Clinician Administered PTSD Scale for DSM-5. Completion of the baseline assessment will take approximately 4 hours and may take place over 1-2 days, depending on the participant's availability. The baseline assessment will be conducted virtually via the HIPAA-compliant telehealth platform Microsoft Teams. All baseline assessments will be audio/video recorded for research purposes and to ensure that assessments were delivered with fidelity.

Study staff will also securely email the full self-report assessment battery to intake participants via REDCap, which takes approximately 40 minutes to complete. Individuals who meet exclusion criteria during the virtual baseline visit or who choose not to participate will be referred for other treatment/resources as indicated.

Setting Up Wearable Device

If eligible for the study following baseline assessments, participants will be mailed a wearable sensor device called a Fitbit to wear on their wrists to measure metrics commonly collected by Fitbit devices (e.g., heart rate variability, heart rate, steps, calories). Participants will be asked to wear the Fitbit between baseline and the six-month follow-up. Following the six-month follow-up, participants will be asked to return the Fitbit device through the mail. Study staff will provide pre-paid shipping labels and shipping instructions at no cost to participants. Participants will not be charged for damaging or failing to return their assigned devices.

Random Assignment of Treatments

Random assignment of eligible participants will occur in two steps using a custom computer randomization algorithm. First, participants will be randomly assigned to receive either two active SGB injections or two placebo saline injections. In the second stage of random assignment, participants will be randomly assigned to receive 1-week of CPT or daily symptom monitoring.

As there will only be three treatment conditions of this study (SGB+CPT, SGB+Daily Monitoring, and Placebo Injection+CPT), individuals that are randomly assigned to the placebo injection group in the first stage of random assignment will automatically be assigned to receive CPT.

Stellate Ganglion Block or Placebo Saline Injections

Depending on which group eligible participants are assigned to, they will either receive an active SGB injection or a placebo saline injection on two separate occasions, with the first occasion occurring before the start of CPT session one and the second occasion occurring two weeks after the first injection. Appointments will take approximately 60 minutes.

Ultrasound-guided SGBs will be performed in the Rush Pain Center by anesthesiologists (AB, SA) who are fellowship-trained in pain management and the use of ultrasound-guided nerve blocks. Participants will be brought to the Rush Pain Center procedure room by a medical assistant who will attach ECG, non-invasive blood pressure, oxygen saturation, and respiratory monitors. Participants will then be allowed to acclimate to the room for 10 minutes. Participants will be moved to a supine position and an IV catheter will be placed. A nasal cannula will be placed in their arm and oxygen will be delivered at a rate of 2 L/min. The anesthesiologists will discuss the procedure with the participant. An ultrasound system will be used to view the anatomy of their neck and needle position. Participants will be placed lying down.

For the active SGB procedure, after aseptic preparation of the skin, and localization of the skin with 1% lidocaine, the transducer will be placed on the neck. 7 mL of bupivacaine (0.5%) will be injected around and into the site of the SG The injection and spread (including longitudinal spread) of local anesthetic will be visualized in real-time. For the placebo saline injection condition, the same procedure will occur, but participants will be injected with 7 mL of saline subcutaneously rather than bupivacaine at the site of the SG.

Virtual CPT or Daily Symptom Monitoring

Between the first and second SGB or placebo saline injection, one-week of virtual massed CPT or daily monitoring will take place.

CPT. Eligible participants so randomly assigned will undergo a course of 1-week-long massed CPT. Massed CPT will be delivered twice per day over five business days (Monday through Friday; 10 sessions total) via the HIPAA-compliant platform Microsoft Teams. Each 50-minute session will closely follow the CPT protocol and will be conducted by a Master's level or higher clinician under the supervision of the principal investigator (PI), who is a licensed clinical psychologist and a certified CPT provider. Participants will not be billed for their CPT sessions.

Daily Monitoring. A daily monitoring condition will be used as a psychotherapy placebo in this study. Participants will have daily appointments with study staff. Study staff will be

trained on how to identify and manage potential distress and will be supervised by the PI. Like at the beginning of each CPT session, participants in the monitoring condition will review their assessments and symptom scores. Study staff will ask participants about the extent to which their assessment scores match their current symptoms, as well as whether participants noticed any changes in their symptoms since the beginning of the study or since the last monitoring session. Study staff will use reflective listening and verbal and non-verbal encouragers but will not use any cognitive behavioral interventions with participants as part of this study condition. Participants will only have one daily monitoring appointment per day for five consecutive days, since measures are only administered once per day during the week. Each session will last approximately 15-30 minutes.

Assessments During Treatment. Both the CPT and Daily Monitoring groups will receive the same daily surveys. These daily surveys will assess PTSD and depression severity and will be administered electronically via REDCap. The completion of these measures takes approximately 10-15 minutes per administration and will be reviewed by study staff.

Virtual Follow-Up Assessments

Participants will be asked to complete self-report measures assessing their PTSD symptoms. Follow-up dates will be calculated based on the date of the second SGB/placebo injection. At the 1-week, as well as the 1-, 3-, and 6-month follow-ups, participants will be asked to participate in virtual structured follow-up assessments that contain the same measures as the virtual baseline assessment. These assessments are intended to assess symptom change throughout the study. Completion of follow-up measures may take approximately 30 minutes for self-report measures and 2 hours for clinician-administered assessments. Following an intent-to-treat design, study staff will make efforts to obtain assessments from all individuals, including those who chose to discontinue treatment as long as participants received at least 1 SGB/placebo treatment and had at least 2 CPT sessions. Participants will be informed about which condition they were assigned to following the completion of their 6-month follow-up assessment.

Treatment Fidelity Ratings

All daily monitoring and CPT sessions will be audio and/or video recorded and an independent fidelity rater with experience in the treatment, who will be a member of the study staff, will randomly select and review 20% of all therapy audio recordings. This process will help ensure that the intervention is provided with fidelity, which will be defined as 80% or more of the maximum possible score on the rating scales. CPT worksheets and homework assignments may be collected and stored for research purposes. Individuals will complete electronic versions of CPT worksheets and upload them to a secure folder accessible only by the individual and study staff.

Measures

Self-report measures and clinician-rated assessments will be used during the study. The assessment schedule below details the different assessment time points for each measure.

Measures may also be administered as needed at clinically relevant intervals. At each follow-up timepoint participants will be asked about any outside psychotherapeutic or medical treatment they have received since starting the study.

Assessment Grid

Life Events Checklist (LEC); Colombia Suicide Severity Rating Scale (C-SSRS); Clinician- Administered PTSD Scale for DSM-5 – Revised (CAPS-5-R); Structured Clinical Interview for the DSM-5 (SCID-5); Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5); Patient Health Questionnaire (PHQ-9); Generalized Anxiety Disorder 7-item Scale (GAD-7); Alcohol Use Disorders Identification Test (AUDIT); Drug Abuse Screening Test (DAST-10); Posttraumatic Cognitions Inventory (PTCI); Heart Rate Variability (HRV); Life Functioning Questionnaire (LFQ); World Health Organization Quality-of-Life Scale (WHOQOL-BREF); World Health Organization Disability Assessment Schedule Version 2 (WHODAS 2.0)

	Baseline	**During CPT or Daily Monitoring**	**1-Wk FU**	**1-Mo FU**	**3-Mo FU**	**6-Mo FU**
Demographics	X					
LEC-5	X					
C-SSRS	X		X	X	X	X
CAPS-5-R	X		X	X	X	X
SCID-5	X		X	X	X	X
PCL-5	X	X	X	X	X	X
PHQ-9	X	X	X	X	X	X
GAD-7	X		X	X	X	X
AUDIT	X		X	X	X	X
DAST-10	X		X	X	X	X
PTCI	X		X	X	X	X
Fitbit Sensor Data	X	X	X	X	X	X
LFQ	X			X	X	X
WHOQOL-BREF	X		X	X	X	X
WHODAS 2.0	X		X	X	X	X
Session Attendance		X				
Session Completion		X				
Adverse Event		X	X	X	X	X

Satisfaction					X	X

Recruitment Methods

Participants will be recruited through the Road Home Program: Center for Veterans and Their Families at Rush University Medical Center and its referral partners such as the Wounded Warrior Project and Warrior Care Network. Participants will also be recruited via Facebook ads, fliers, and word-of-mouth at local VA Medical Centers, of which there are three in the Chicagoland area alone. The Road Home Program has strong relationships with these VAs and frequently receives direct referrals for massed PTSD treatment. We will utilize the teams' relationships with different local and national VA leaders to disseminate information about the proposed project to enhance recruitment. In addition, our team has extensive experience recruiting for PTSD treatment trials in civilian populations using phone-based "on hold" advertising and social media advertisements.

To complement these recruitment strategies, we will also be engaging a clinical trial recruitment firm (e.g., TrialFacts). The recruitment success will be evaluated on an ongoing (quarterly) basis. Changes to the recruitment strategies will be discussed among the study team should problems be encountered.

Compensation for Participation

Participants will be compensated for the completion of study-related assessments in the form of Amazon electronic gift cards emailed to participants. Participants will be compensated up to $330 for completion of all study tasks, which breaks down to $40 for the baseline assessment, $40 for the 1-week follow-up, $50 for the 1-month, $100 for the 3-month, and $100 for the 6-month follow-up assessments.

In compliance with federal regulations, service members and federal civilian employees cannot be compensated for completing study procedures while on active duty.

Participants will not be compensated for the treatment they receive or the daily surveys, which are part of measurement-based care and considered a part of treatment.

Baseline	1-Week Follow-Up	1-Month Follow-Up	3-month Follow-Up	6-month Follow-Up
$40	$40	$50	$100	$100
				Total: $330

Costs to Participants

There will be no direct cost to participants to participate in this study. All clinical, professional, diagnostic and laboratory services related to the study will be provided at no cost to participants. There will be no medication costs to participate; medication (SGB medication or placebo saline injection) will be provided to the participants at no cost. However, participants will be responsible for their phone service provider's standard charges as they apply to any study-related phone calls and internet usage. They will also be responsible for any costs related to transportation to and from the Pain Clinic, including parking.

Risks to Participants

There are risks associated with the SGB procedure as well as with CPT and Daily Monitoring; these risks are outweighed by the potential benefits of this study.

Risks Associated with SGB

SGB injections are typically well-tolerated but can be associated with risks. Potential serious complications associated with the SGB procedure include vascular puncture, neural puncture, pneumothorax, thyroid injury, esophageal and/or tracheal puncture, and intravascular injection, neuraxial, phrenic nerve or brachial plexus spread of local anesthetic, and infection.

Other common risks following SGB treatment are bruising or soreness at the injection site, nasal stuffiness, hoarse voice, feeling a "lump" in the throat, and difficulty in swallowing. A transient but potentially troubling common complication of an SGB is an ipsilateral Horner syndrome (ptosis, miosis, enophthalmos, facial anhidrosis, and conjunctival injection) These mild symptoms are short-lived and in almost all cases resolve within hours. Although Horner's syndrome occurred in 70% of the subjects in one SGB study by McLean, it did not appear to impact the patients' decision regarding acceptance or willingness to repeat the procedure. Participants may experience hoarseness which should disappear within 4-6 hours. Overall, they found that 100% of the patients were satisfied with the SGB and were willing to undergo repeated procedures as necessary

In a randomized controlled trial of 74 patients that underwent SGBs, only 3 (2%) reported adverse events. None of the complications were serious and included temporary laryngeal irritation, pain at the injection site, and a brief self-reported bradycardia. There has been no reported incidence of a severe adverse drug reaction to the study treatment in any published literature examining SGBs for PTSD.

Risks Associated with CPT and Daily Monitoring

CPT is an existing evidence-based treatment for PTSD that has been shown to be both effective and safe. Some individuals experience temporary emotional distress when discussing their traumatic experiences. This distress is usually temporary and subsides after the discussion of the trauma concludes. Daily Monitoring has been safely used as an active control condition in various research trials and has been shown to reduce distress. To date, no adverse events have been associated with CPT or Daily Monitoring in either massed or spaced formats, suggesting both are tolerable.

Management of Risk

The risk for serious complications associated with a SGB procedure will be managed through the use of ultrasound guidance. When placed using ultrasound guidance, SGB has been shown to have a high safety profile. Subjects will be asked to refrain from eating from midnight the night before the procedure and only be allowed sips of water the morning of the procedure. Subjects will be instructed not to drive or operate heavy machinery for 24 hours after the

procedure. Subjects will be instructed not to eat food or drink for four hours after the procedure or until their ability to swallow as normal has returned. If the study physician deems the risks associated with the SGB treatment to be too severe for the participant, the study physician may, in correspondence with the PI, remove the participant from the study.

Participants may experience distress during CPT treatment or Daily Monitoring. Participants' suicidality will be assessed by the treating clinicians on an ongoing basis and assessed formally at the baseline as well as each follow-up time point using the Columbia Suicide Severity Rating Scale (C-SSRS). If a participant indicates having "Thoughts that [they] would be better off dead or of hurting [themselves] in some way" more than half the days (2) or nearly every day (3), the study clinician will conduct a safety assessment. If any participant becomes actively suicidal with intent, the study clinician will refer the participant to a higher level of care (i.e., psychiatric, medical, or emergency services).

All treatment sessions/visits will take place during regular business hours; in the case of a crisis during treatment or a virtual assessment, the study clinician will be available to assist or instruct the participant to call 911 or go to their nearest emergency room. Participants will be responsible for the cost of such care. Prior to the start of any telephone/video session, the provider will inquire about the current location to have this information in case of an emergency. In addition, we will obtain the number of a person whom they trust at the beginning of treatment who lives nearby (i.e., 20-minute drive max). Participants can agree that we call these individuals to check on the participants when needed before we ask the local police department to conduct a wellness check. Individuals will no longer be able to continue this course of CPT or Daily Monitoring if they are actively suicidal but may be able to enroll at a later time after reaching stability per eligibility requirements.

The risk of loss of confidentiality, although unlikely, is possible. All study staff will work diligently to ensure that all data is stored securely and that study-related files are password protected so that only members of the study staff will have access to identifiable data. To protect confidentiality, each subject is assigned a unique code. Only study personnel will be able to link a patient's name to the identification number. All telephone/video sessions will be conducted using a HIPAA-compliant platform, Microsoft Teams. In addition, a Certificate of Confidentiality has been obtained. No identifiable data will ever be disclosed to any outside parties, except where required by law. De-identified data may be reported in aggregate for internal clinical use, publications, or other presentations.

A Certificate of Confidentiality has been obtained as part of this study. This Certificate means that researchers cannot be forced, even by courts or the police, to disclose any information about participants. The Certificate does not stop participants from disclosing, or agreeing in writing to allow researchers to disclose, information about them. The researchers may not disclose or use any information, documents, or specimens that could identify participants in any civil, criminal, administrative, legislative, or other legal proceeding, unless participants consent to it. Information,

documents, or specimens protected by the Certificate of Confidentiality may be disclosed to someone who is not connected with the research if:

1. There is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases);
2. They consent to the disclosure, including for medical treatment;
3. It is used for other scientific research in a way that is allowed by the federal regulations that protect research participants;
4. A governmental or funding agency requests it for auditing or program evaluation purposes.

If a participant discloses actual or suspected abuse, neglect, or exploitation of a child, or disabled or elderly adult, the researcher or any member of the study staff must, and will, report this to Child Protective Services (such as the Department of Family and Human Services), Adult Protective Services, and/or the nearest law enforcement agency.

Potential Benefits to Participants

Participants in this study may experience direct benefits. CPT has been shown to be effective for the treatment of PTSD. Thus, participants in this study may experience substantial reductions in their PTSD symptoms (as well as other comorbid mental health conditions). Together, these improvements can result in improved quality of life by being able to re-engage in daily functions.

The knowledge gained from this project may improve our understanding of the mechanisms underlying successful PTSD treatments, potentially informing the development of more targeted and effective therapeutic strategies for individuals with PTSD. One contribution toward that goal is studying the effectiveness of a novel PTSD treatment (SGB), which may reduce symptom severity and improve life functioning. The knowledge gained from this project is also important because it can be used to inform VA and DOD clinical practice guidelines regarding the use of SGB and massed CPT.

Data Storage

Specify the site at which the data will be stored and how it will be stored: Audio recordings, video recordings, copies/scans of CPT session materials, and all electronic data collected through REDCap-delivered self-report assessments will be de-identified, password-protected, and stored in a restricted folder within the RUMC secure network infrastructure. Telephone/video visit audio and video recordings from the HIPAA compliant telephone/video platform will be uploaded to the secure server within one business day and will be deleted from the platform immediately upon upload. CPT worksheets electronically uploaded to the secure folder accessible only to the participant and study staff will be deleted from this folder following the participant's final study visit. Copies of the worksheets will be saved to a separate restricted study folder on the RUMC network infrastructure. When personally identifying data cannot be

removed (as may be the case with audio or video files), they will be provided with a unique de-identified code and stored in a separate and secure network location.

How long will the data be maintained and/or stored? All electronic data collected will be stored for least 5 years after the completion of the study. Once all analyses have been conducted after at least 5 years, all data will be securely deleted from the secure, password-protected file and system. Who, other than the specified study team, will have access to the study records or data? Specify their name, role, and affiliation. The principal investigator will monitor all access to data. Only study staff listed on and approved by the IRB will have access to the data for research purposes. Audio and/or video recordings may be shared with approved external collaborators for analysis through encrypted software shared on a secure web-based storage site. Participants in audio and/or video recordings will be identified by coded subject IDs.

Justify your needs to collect PHI in this study: PHI will be collected in order to characterize the participant sample and to maintain contact with participants throughout the study, deliver assessments, and document the treatment progress. Audio and video recordings may also contain PHI that can potentially identify respondents. As PHI cannot be removed from audio and video files, these files will be provided with de-identified codes and stored in a separate and secure network location.

Describe how and where PHI will be destroyed following the completion of the study: Not applicable. No identifiable data will ever be shared by the study team with personnel outside of the approved study staff. Any data shared with other researchers will be de-identified. All the findings in this study will be de-identified or reported at a group level or in aggregate with no risk of identifying individual participants. Will subjects be able to request that their information be removed from the data bank? Yes. However, it may not be possible to withdraw or delete materials or data in the event that they have already been shared with other researchers.