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A randomized controlled trial of yoga vs nonaerobic exercise for veterans with PTSD: Understanding efficacy, mechanisms of change, and mode of delivery

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ABSTRACT

Background and objectives: Posttraumatic stress disorder (PTSD) is a chronic, disabling, and prevalent mental health disorder among Veterans. Despite the availability of empirically supported psychotherapies, many Veterans remain symptomatic after treatment and/or prefer to seek complementary and integrative health approaches, including yoga, to manage PTSD. The randomized controlled trial (RCT) described herein will evaluate the efficacy of a manualized yoga program as compared to nonaerobic exercise in reducing PTSD severity among Veterans. A secondary aim of this study is to better understand the mechanisms of change.

Methods: Veterans (N = 192) with PTSD will be randomized to hatha yoga or nonaerobic physical activity control; both groups consist of 12 weekly, 60-min group or online training sessions with 15–20 min of daily at-home practice. Outcome measures will be administered at baseline, mid-treatment, posttreatment, and 12-week follow-up.

Projected outcomes: This study will evaluate changes in PTSD severity (primary outcome) as well as depression, anxiety, anger, sleep problems, and psychosocial disability (secondary outcomes). We will also use multiple mediation to examine two potential models of the mechanisms of clinical effect: the Attention Model (i.e., yoga increases attentional control, which reduces PTSD symptoms), the Coping Model (i.e., yoga increases distress tolerance, which improves coping, which reduces PTSD symptoms), and the combination of these models. This aspect of the study is innovative and important given the absence of an existing, comprehensive model for understanding yoga's impact on PTSD. Ultimately, we hope to develop guidelines for application of yoga to PTSD recovery.

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1. Introduction

Posttraumatic stress disorder (PTSD) is a chronic, debilitating disorder that broadly impacts affected individuals. The VA/DOD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder [1] recommends individual manualized trauma-focused psychotherapy as the first line treatment approach. Although these therapies effectively reduce PTSD symptoms, most patients continue to have a diagnosable disorder after treatment [2]. Others seek alternatives to psychotherapy and pharmacotherapy based on individual preferences [3]. VA facilities offer an array of complementary and alternative approaches [4], but there is a paucity of evidence about their effectiveness [5]. Although yoga is the most commonly used complementary intervention among adults in the US [6], there is insufficient evidence to recommend it for treatment of PTSD [7]. A recent meta-analysis found that yoga outperforms no treatment but not attentional controls in terms of reduction in PTSD symptoms, but findings were highly variable and the extant studies were of inconsistent quality [8], highlighting the need for additional high quality research in this area. Most studies in Veterans to date have been small and/or uncontrolled [9–11]. The exception is a large trial comparing yoga to a wellness control, which found small-medium effects favoring yoga at post-treatment [12]. To date, however, yoga has not been compared to other types of physical activity in terms of impact on PTSD symptoms. The purpose of this manuscript is to describe the rationale, objectives, methods, and theoretical and pragmatic issues in conducting a randomized controlled trial (RCT) of yoga as compared to a non-aerobic physical activity control for Veterans with PTSD.

Effective psychotherapies are designed based on conceptual understanding of processes that create or maintain psychopathology and the application of techniques to modify important mechanisms. Similarly, the study of yoga-based interventions should seek to elucidate mechanisms of change that underlie the treatment response; an additional goal of this paper is to describe the potential mechanisms of change that will be explored in this study.

Attentional model. One potential model of change is based on cognitive abnormalities observed with PTSD. In particular, PTSD has been linked to impaired attention regulation and inhibitory control [13–16]. We have previously hypothesized that such deficits in executive functioning contribute to difficulty regulating cognitions and emotions, sustaining PTSD. We further suggested that remediation of such deficits may help to resolve PTSD symptoms [17]. Yoga may represent a form of cognitive training insofar as it provides practice in attentional control. Yoga involves active and deliberate regulation of attention to the breath or to a fixed point [18]. Because other techniques that provide repeated practice with allocation of attention, such as focused attention mindfulness, have been linked to enhanced attentional functioning (e.g. Refs. [18,19], we hypothesize that yoga may influence PTSD symptoms by building attentional control (refer to Fig. 1).

Coping model. An alternative model is motivated by findings that PTSD is driven by maladaptive coping processes, such as impaired emotion regulation and increased rumination, thought suppression and experiential avoidance [20]. We hypothesize that yoga may build one's capacity to regulate emotions [21] by increasing tolerance of discomfort. This has been demonstrated in a laboratory setting; individuals with extensive experience with yoga have been shown to tolerate induced pain about twice as long as controls without a yoga practice [22]. This has also been demonstrated in a clinical sample; Medina et al. [23] showed that hatha yoga increased self-reported distress tolerance, which in turn led to less emotional eating, in a sample of women who were identified as having difficulty in this area. A direct extension of these data is diagrammed in Fig. 2. We will examine the model that yoga increases tolerance of discomfort, which improves coping, which in turn reduces PTSD symptoms. To inform future work, we additionally will explore whether a combination of the Attention and Coping Models explains more variance than either one alone.

2. Materials and methods

2.1. Research design

This study is an RCT of Hatha yoga as compared to a nonaerobic exercise control condition. A sample of 192 participants will be recruited to have at least 144 completers (25% attrition). Longitudinal outcome assessments will take place over the active treatment period (14 weeks) and a 12-week follow-up. The follow-up is planned because a previous trial suggested that ongoing practice is critical for continued clinical effects [24], so replication of that finding has important clinical implications.

2.2. Participants

Participants will be Veterans with a diagnosis of PTSD or subsyndromal PTSD accompanied by distress and impairment, aged 18 or older, who are able to consent and willing to participate. Co-occurring disorders such as depression, anxiety, or treated substance abuse or dependence problems are permitted provided that PTSD is the primary presenting complaint. There is no restriction as to the type of trauma experienced. Heterogeneity within the group of Veterans (e.g., gender, era of service, type of trauma) is allowed for greater generalizability of the results from this sample as well as to facilitate recruitment. Trauma sensitive principles [25] will be employed to maximize participants' comfort, particularly for individuals with concerns about personal safety/bodily integrity. The following are criteria for exclusion: (1) serious suicidality or homicidality that has required urgent or emergent evaluation or treatment within the past three months, (2) a known, untreated substance abuse or dependence problem (inclusion is possible if there is evidence that the individual has been afforded and is complying with treatment for the substance problem), (3) serious mental disorders, such as psychotic disorders or bipolar type I, or serious dissociative symptoms, (4) cognitive impairment that would interfere with treatment, (5) circumstances that lead to recurrent traumatization (e.g., engaged in a violent relationship), (6) any medical condition for which yoga or exercise is contraindicated and pregnancy, and (7) concurrent enrollment in any other treatment specifically targeting PTSD symptoms or any meditative or mind-body intervention (including yoga practice >1 class/month in the preceding 6 months). Participants can continue current pharmacological treatment, provided they have

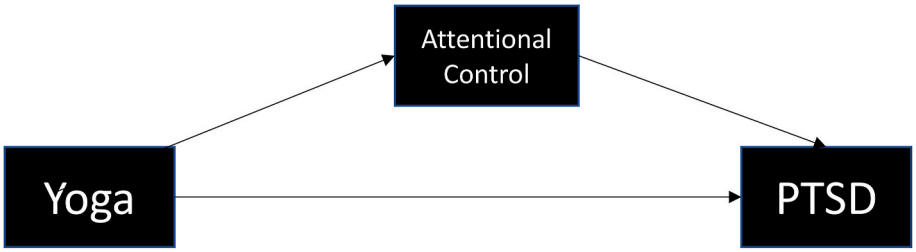

Fig. 1. Proposed multiple mediation of the impact of yoga on PTSD via mindfulness and attentional control.

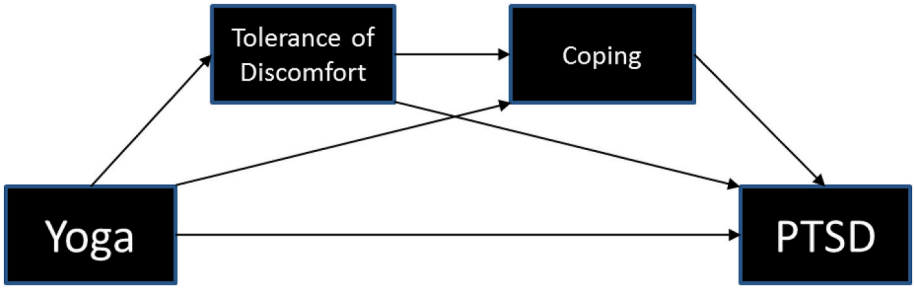

Fig. 2. Proposed multiple mediation of the impact of yoga on PTSD via tolerance of discomfort and coping.

stabilized on medication, i.e., no additional treatment response is expected, and no changes are anticipated during the study period. Ongoing supportive or nonspecific therapies are allowed as well. These selection criteria are intentionally broad to represent as fully as possible Veterans who may seek alternative interventions for their PTSD. The sample may have limited generalizability to non-military populations.

2.3. Study procedures

The study procedures are approved by the Institutional Review Board (IRB) at VA San Diego Healthcare System and overseen by the VA Clinical Science Research and Development (CSR&D) Data Monitoring Committee.

Potential participants will be recruited from VA clinics and the community. Community recruitment will include placing advertisements in places frequented by Veterans (e.g., Veterans Centers on local college campuses) and where people may seek alternative interventions (e.g., health food store bulletin boards, targeted publications), and providing information through local Veterans' groups and word of mouth. The initial contact for potential participants will be with a study recruiter/assessor, who will complete informed consent and conduct the evaluation for eligibility. After eligibility and consent are confirmed, the participant will complete assessments at baseline, 6 weeks, 12 weeks and 24 weeks (a 2-week grace-period is allowed around all assessments after baseline). Evaluation of safety will take place on a weekly basis. Participants will receive a payment for each major data collection point ($75 at each of baseline and post-treatment and $100 for follow-up for a total of $250). Randomization will be done by the study statistician with 2:1 allocation to yoga. Randomization will follow the baseline assessment and take place at the individual level via pre-sealed envelopes.

The COVID-19 pandemic began during the first year of recruitment for the study (approx. 15% of the sample had been enrolled prior to the need to stop in person activity). The pandemic necessitated a change to entirely remote procedures, including documentation of informed consent, data collection, and intervention delivery. Because of the need to conduct all assessments remotely, we had to use alternative versions of some tasks and to remove those that can only be conducted in person or that require precise timing (refer to Measures). We plan to resume in person study activities when possible, likely allowing for some remote procedures (e.g., completion of self-report measures, make-up classes) to promote retention.

2.4. Measures

Instrument selection for this trial was based on psychometric properties, past use with mental health populations and/or yoga, conceptual fit with our model, and minimizing participant burden. The sample will be characterized at baseline in terms of relevant demographic characteristics (age, gender, race/ethnicity, relationship status, years of education, SES/income/living situation, occupation/work status, branch of service/highest rank, service connection/disability status).

2.4.1. Eligibility

Individuals with a PTSD Checklist – 5 (PCL-5 [26]; score of 33 or greater, the currently recommended cutoff for the instrument [80], will be eligible for enrollment. Individuals with lower initial PCL-5 scores may still be eligible if they meet criteria for PTSD or subsyndromal PTSD (criterion A and B plus one additional criterion) using the Clinician Administered PTSD Scale for DSM-5 (CAPS-5 [26]; refer to 2.4.2). Suicidality, substance dependence, and serious mental illness will be evaluated using the Mini International Neuropsychiatric Interview (MINI 7.0; [27], which has been validated against other validated structured interviews. It will be supplemented with questions to assess homicidality. The Montreal Cognitive Assessment[1] (MoCA [28]; is a brief (~10 min) clinician-administered cognitive screening test, which will be used to screen for cognitive impairment. If the score is < 22, which has been identified an as appropriate cutoff for psychiatric patients [29], patients will be referred for additional evaluation and excluded, unless a qualified clinician provides clearance to participate. The blind version of the MoCA, which is the same as the MoCA except for the removal of visual items, is used for remote assessments. The Life Events Checklist portion of the CAPS-5 will describe the type and number of traumas to which an individual has been exposed, including identifying current circumstances that may preclude study involvement. Ability to tolerate exercise will be assessed using a Pre-Exercise Screening Tool. Finally, the participant will be queried about use of mental health services, including pharmacotherapy, psychotherapy (type, modality, frequency and duration), complementary and alternative approaches and hospitalization using a modified version of the Emory Treatment Resistance Interview for PTSD (ETRIP; [30].

2.4.2. Primary outcome

The CAPS-5 [26] will be used to establish the PTSD diagnosis and quantify severity. This clinician-rated measure of PTSD is the "gold standard" for assessing PTSD. It has high internal consistency (for the DSM-IV version, alphas of 0.87 and 0.88 for the three PTSD symptom clusters and 0.95 for PTSD symptoms overall) and validity (sensitivity, specificity, efficiency, and agreement). The CAPS will be administered by a trained assessor who is blind to treatment condition, and the total score will be used as the primary measure of clinical outcome.

2.4.3. Secondary outcomes

Given our interest in exploring the effect of these interventions on symptoms that commonly co-occur with PTSD, we will also assess the following additional outcomes. Depression severity will be measured by the Patient Health Questionnaire depression items (PHQ-9; [31]. The PHQ-9 has strong internal consistency (0.74-0.81), validity, and demonstrated responsiveness to change [32]. General anxiety will be measured by the 40-item State-Trait Anxiety Inventory (STAI; [33]. In clinical samples, the STAI has strong internal consistency (0.94) and test-retest reliability (0.93) and corresponds highly with other measures of anxiety [34]. Anger will be measured by the 35-item State-Trait Anger Expression Inventory – II (STAXI-II; [35]. The internal consistency of the STAXI-II subscales ranges from 0.72 to 0.96 in psychiatric patients and

has strong convergent and divergent validity [36]. Sleep problems will be quantified using the Insomnia Severity Index (ISI; [37], a 7-item instrument that assesses the consequences of and distress related to insomnia. The internal consistency of the ISI is 0.74, reflecting some heterogeneity among the items. The measure has a moderate correspondence to measures of sleep quality as derived from sleep diaries but is considerably less burdensome [37]. Pain will be assessed using the PROMIS pain intensity, pain interference and physical function scales [38]. These measures have been shown to detect intervention-related change in heterogeneous pain groups [39]. Finally, the Sheehan Disability Scale (SDS; [40], a 3-item measure of impairment in work, social, and family settings, will be included. This widely used but low-burden measure of disability has been shown to change with treatment in similar population samples (e.g., Ref. [41].

2.4.4. Safety measures

The PCL-5 and PHQ-9 will be administered prior to every in person session, as is typical practice for PTSD interventions in the VA. Additionally, the Alcohol Use Disorders Identification Test (AUDIT [42]; will be used to track problematic alcohol use and a post-exercise survey will be used to injuries related to the interventions. After the onset of the pandemic, a study nurse began calling participants each week to administer these measures, and the CAIR Pandemic Impact Questionnaire (unvalidated measure available from the first author) was added to assess pandemic-related stressors, mental health changes and perceived growth.

2.4.5. Mechanistic Variables[1]: Attention Model (Fig. 1)

The hypothesized link between yoga and attention is through repeated practice of focused attention during classes. Two measures will be used to quantify the extent to which the skill is developed in the course of the study. The present-moment awareness subscale of the Philadelphia Mindfulness Scale (PMS [43]; will be used to quantify attention to the present moment. The PMS has good internal consistency (Cronbach's α 0.75) and validity (e.g., corresponds highly with other measures of mindfulness but not with measures of psychopathology or social desirability) in psychiatric samples. A mindful breathing task, wherein participants are instructed to focus on their breath for an undisclosed period and prompted at unpredictable intervals to indicate whether their focus was on the breath or elsewhere, will be included as an objective measure of capacity for focused attention to breath. This task is positively associated with mindfulness and negatively associated with measures of rumination, repetitive thinking, fear of bodily sensations and depression [44].

To characterize the nature of yoga's impact on attention, we will utilize two tasks with an affectively neutral context, as well as two tasks that include affective stimuli to allow for an assessment of the ability to deploy attentional resources in emotional contexts. The Digit Span test from the Wechsler Adult Intelligence Scale 4th edition (WAIS-IV) will be used as a standardized neuropsychological measure of attention and working memory [45]. This test includes Digit Span Forward, wherein the participant is read a sequence of numbers and recites the numbers back in the same order; Digit Span Backwards, wherein the participant is read a sequence of numbers and must recite them back in reverse order; and Digit Span Sequencing, wherein the participant is read a sequence of numbers and must recite them back in numerically ascending order. Digit Span is a well validated assessment with established norms and has been shown to be sensitive to change in a study using a yoga intervention [46]. Each raw subtest subscore is calculated based on the number of items correctly recited on each trial. Guidelines are available to allow for remote administration of this measure, and modality of administration has been shown not to affect performance [47]. The Attentional Network Task (ANT) is a commonly used computerized visual attention task [48]. During the task, participants are asked to identify the direction that a central target arrow points. On either side of the target arrow are flankers that serve as potential visual distractors. The direction of these flankers can be congruent (arrow the same direction as the target), incongruent (arrow the opposite direction of the target), or neutral (no arrow). On some trials - prior to presentation of the target arrow and flankers - cues are presented that can indicate the position of the upcoming target (orienting), the opposite of the position of the upcoming target (disengagement), or in the center. Thus, the ANT is comprised of seven discrete conditions consisting of combinations of four cue conditions and three flanker conditions. Outcomes include reaction times for each condition, corresponding to the respective attentional network processes, with lower reaction times indicative of better attention control performance. A recent study found that the ANT task detected changes in attentional functioning associated with hatha yoga practice [49]. In order to evaluate attentional capacity under internally generated affective context (e.g., frustration, stress), the computerized adaptive Paced Auditory Serial Addition Task (PASAT) will be used. In this task, participants are presented with single digits aurally. The participant is instructed to add each new digit to the preceding digit and note the correct result using computer interface, receiving feedback after each trial. The time available to compute the answer will begin at 3 s, then decreases on an adaptive schedule based on task performance, leading to decreasing available response time and increased error rates. The task has been shown to reliably assess both attentional control processes [50] and to evoke stress in laboratory studies [51]. The task will allow for an evaluation of the ability to utilize cognitive resources in the face of negative affect. Mean decision time allowed is used as an index of performance. To evaluate attentional control in the presence of external affective context the emotional Stroop task (eStroop) will be used. The eStroop is similar to the original Stroop task [52], which requires participants to label the color of ink that color names are printed in. In the eStroop, the printed word is neutral in valence (e.g., 'pencil') on some trials and affectively valenced (e.g., 'attack') on other trials. The eStroop is designed to evaluate the influence of emotional content by manipulating the valence of the to-be-ignored word and testing for any changes in performance. Extant data demonstrate that individuals with anxiety and PTSD have delayed response times for color naming of emotional words compared to neutral words [53,54]. Attention control mechanisms involved in the orienting, maintaining, and shifting of attention are thought to determine the degree to which emotional information detrimentally impacts performance by altering attention from task demands [55,56]. Shorter reaction time latencies reflect greater attention control, and lower discrepancy between neutral and affective trials indicates a lower impact of emotion on performance. Because of the precise timing required for the ANT, PASAT and eStroop, these cannot be administered remotely.

2.4.6. Mechanistic Variables[1]: coping model (Fig. 2)

We hope to identify a latent variable indicating maladaptive coping strategies that are associated with PTSD based on the following potential indicators. The Ruminative Thought Style Questionnaire (RTSQ) is a 20-item, Likert-based (1–7) scale with good psychometric properties (Cronbach's α 0.92, strong correlations with measures of depression, anxiety and repetitive thought) and demonstrated separability from mood [57]. The Emotion Regulation Questionnaire (ERQ [58]; is a 10-item measure of reappraisal and expressive suppression, which are thought to be effective and ineffective emotion regulation strategies respectively. The ERQ expressive suppression subscale has previously been shown to be impacted by yoga in PTSD patients [21] and has good convergent and discriminant validity and internal consistency [58]. Experiential avoidance will be quantified using the Brief Experiential Avoidance Questionnaire (BEAQ; [79]). This 15-item Likert-based (1–6) measure was developed to improve upon the Acceptance and Action Questionnaire – II (AAQ-II), which has been shown to be highly reflective of general distress [59]. The BEAQ has good internal consistency (Cronbach's α 0.86) and is more strongly related to measures of avoidance than negative affect.

Our model also predicts that tolerance of discomfort will contribute

to the coping model. To assess this, we will use the Distress Tolerance Scale (DTS), a 15-item, Likert-based (1–5) scale with good internal consistency (Cronbach's α 0.75) and adequate test-retest reliability ($r = 0.61$). The DTS has been shown to be associated with PTSD [60], prospectively predict problematic alcohol use [61] and improved by Hatha yoga [23]. In addition, cold pain tolerance will be used as an objective measure of tolerance of discomfort, as in the Villemure et al. [22] study, which showed greater pain tolerance associated with yoga practice. Each participant will complete two hand immersions in a cold-water bath (Thermo Scientific, Waltham, MA) at 5 °C (±0.1°) with a 3-min intertrial interval. Participants will be instructed to place their hand in the cold-water bath up to their wrist until they can no longer tolerate the pain, with a 2-min immersion maximum (though participants will not be informed of this prior to the trials). Cold pain tolerance will be measured as the time at which participants remove their hand from the cold water. Immediately after removing the hand from the cold water, participants also will provide verbal ratings of pain intensity and unpleasantness on a scale of 0 (no pain sensation/unpleasantness) to 100 (the most intense/unpleasant pain imaginable). The cold pressor was eliminated for remote participants.

2.4.7. Physiological Variables[1]

When assessed in person, participants will wear an Empatica™ Watch, which is a physiological monitoring telemetry device, for a 5-min acclimation period (visual puzzles), during the attention, mindful breathing, and cold pressor tasks and then for a final 5-min recovery period. The device stores and transmits vital signal data including pulse oximetry (for heart rate), respiration rate, galvanic skin response, and temperature. Cardiac data will be sampled at a frequency of 64 Hz using a red and green frequencies to aide in peak detection by subtraction of difference of light between oxygenated and non oxygenated peaks, processing in R (R packages: wmtsa and rhrv) for RR interval calculation and then passed to Kubios for secondary subject level processing [62]. The logistics of providing the device to remote participants made this task infeasible during social distancing.

The primary physiological outcome of interest is reduced heart rate variability (HRV). HRV, which quantitatively assesses variation in heartbeat intervals, is used to gauge psychological distress, such as PTSD [63] and changes in autonomic function, with HRV reflective of vagal tone (parasympathetic activity; [64]. Both yoga and physical activity increase HRV [65,66], and improve autonomic balance [67], e.g., leading to increased high frequency (HF) and decreased low frequency (LF) cardiac activity [68]. Digitized electrocardiogram (ECG) data will be analyzed to detect the R-wave peaks of the QRS complex and R-R intervals. Artifacts and ectopic beats will be manually replaced using interpolation. The objective will be to quantify HRV indices of parasympathetic cardiac control using measures from time and frequency domains. The objective will be to quantify HRV indices of parasympathetic cardiac control using measures from time and frequency domains during the periods of rest and recovery. Because HRV is hypothesized to be affected by both interventions, this measure can be considered an index of the equivalence of the interventions in terms of anxiety-relevant physical conditioning. HRV may become a covariate, particularly in relation to the coping model, to the extent that it is differentially impacted by the interventions.

2.4.8. Compliance

Engagement in the interventions will be tracked via class attendance or reported use of online materials. A weekly diary will be used to collect information about at home practice and other physical activity, and summative measures will be used to track continued physical activity during the follow-up period.

2.5. Treatment conditions

2.5.1. Hatha yoga

Yoga is an ancient system of physical postures (asana), breath (pranayama), meditation, and self-awareness. Veterans will be guided through the same standardized yoga protocol each week, detailed below. The yoga program is the Level 2 Inner Strength protocol created by Connected Warriors, a national organization disseminating trauma-conscious yoga classes and teacher training to Veterans and active duty military personnel (https://connectedwarriors.org). This protocol was selected, in part, because it is already utilized in 32 VA medical centers and Vet Centers, 16 active duty military installations, and online. This sequence consists of 34 postures and is intended to establish a mind-body connection, with a mindful present-centered focus, through conscious breathing synchronized with stillness or movement.

Each yoga class begins with a theme (adapted from Ref. [69], which is an idea to focus on during the yoga practice (e.g., "welcoming in all aspects of experience"), and we will consistently encourage Veterans to apply these ideas "off the mat," in their daily lives. The Veterans are then guided into a resting pose for conscious breathing. A strength and movement warm-up sequence follows, beginning with spinal movement (cat and cow poses), core activation (tiger pose), a common yoga progression of plank, downward facing dog, chaturanga to a gentle back bend (sphinx pose), and a modified sun salutation. The protocol continues into several warrior poses and a balance pose (tree pose). Finally, there is a progression of seated poses (e.g., supine twist, happy baby) as a cool-down. The poses will be presented with several recommended modifications for varying ability levels or to safely accommodate past injuries. The class ends with a three-to-five minute final resting meditation, called savasana.

2.5.2. Nonaerobic exercise

The exercise control condition was designed to meet the physical activity guidelines [70] for muscle strengthening and flexibility exercise. The manualized full-body stretching-strengthening class will be held in 60-min sessions once weekly for 12 weeks, with home conditioning focused on a specific body region (arms, legs, trunk, or full body) for 15–20 min per day, matching the time spent in yoga practice. No yoga postures, breathing, or meditative instruction will be included in the control exercise program, and both intervention groups will receive comparable levels of social interaction during group instruction. Each exercise class will consist of a warm-up, strengthening exercises, and cool-down periods. The warm-up and cool-down periods will comprise 30-s static stretches for all major muscle groups targeted by the Hatha yoga intervention. Full body strengthening exercises will offer three levels of difficulty, beginning with bodyweight only and progressing toward greater resistance with hand weights or bands. Participants will be instructed to perform as many repetitions as possible at a moderate, self-selected pace during a 30-s work interval for each exercise. Participants will add resistance when they are able to perform continuous repetitions for the full 30-s with correct form and no rest breaks, while maintaining a Rating of Perceived Exertion (RPE) of $<4/10$ (moderate to somewhat hard) on the modified Borg Scale. Modifications for each exercise will be offered to accommodate any physical limitations and ensure the safety of individual participants. Consistent with current recommendations for yoga trials, an active control group was selected to control for the non-specific effects of exercise on PTSD symptoms. The stretching-strengthening program was designed by a doctoral-level physical therapist to match physical demands of the Hatha yoga intervention, including low-load resisted movements and end-range static postures to promote improvements in muscle strength/endurance and flexibility, but not aerobic capacity. This type of exercise program was previously shown to be comparable to Hatha yoga in terms of gains in functional fitness [71] but less effective at improving cognition [72] in community-dwelling samples of older adults. To match the structure of the yoga class, the active control group also includes a "theme" at the

beginning of the class, like hydration or the benefits of stretching.

2.5.3. Virtual classes

At the onset of the COVID-19 pandemic, we created video recordings of classes. Participants will be provided with secure links to access the pre-recorded class to which they are assigned, and study staff will attempt to contact them on a weekly basis to collect data on class attendance, encourage compliance, and collect safety measures. We plan to begin offering live remote classes as well.

2.5.4. Training and supervision of instructors

The instructors, who teach both types of class, will be certified (minimum of 200-h yoga teacher training; [82]) and trained in trauma-sensitive yoga principles, which is a set of adaptations to enhance the comfort of trauma survivors when yoga is delivered in a group setting. Trauma-sensitive practice involves using invitatory (as opposed to commanding) language, providing a space where clients feel less vulnerable (e.g., lighting should not be too dark), allowing patients to opt out of postures, minimizing physical assists until trust is established, and creating an overall welcoming and approachable environment [25]. Additionally, both instructors will receive training from a physical therapist on safe technique and progression, and on individualized modification of exercises/poses and use of props to support those with physical limitations.

Fidelity to the manual will be assessed using a standardized treatment fidelity checklist for each intervention. Ten percent of yoga and stretching-strengthening exercise sessions will be randomly selected for onsite review by a licensed physical therapist. Sessions will be rated using an adherence checklist for each procedure or instruction. Instructors will receive written and verbal feedback to prevent drift and ensure consistent delivery of the intervention between instructors and across time.

2.6. Data analytic plan

2.6.1. Sample size

The sample size was estimated based on the primary analysis, which will compare CAPS change from baseline to post-intervention between two intervention groups. Medium effect size was selected based on finding from previous yoga trials [73] and was defined as a between-group difference increasing linearly from 0 at baseline to 0.5 SD units at post-intervention. We assumed a correlation coefficient of 0.8 between the repeated measures of the outcome. On this basis, we proposed a total sample size of 144 completers to achieve a minimum 80% power to detect the significant difference in CAPS change between two study interventions. We will attempt to enroll 192 Veterans, allowing for 25% attrition, which would not be unusual for this population.

2.6.2. Clinical outcomes and baseline variables

The distribution of study variables will be examined by descriptive statistics (means, standard deviations, quartiles, frequency, proportion) and graphs (boxplot, histogram and bar plot) overall as well as by study intervention. Variables will be included as covariates in the model to account for pre-existing group differences or factors that are known to be associated with outcomes (e.g., age and cognitive measures). Randomization will be tested by performing a series of Wilcoxon rank sum tests and Chi-square/Fisher's exact tests to compare demographic and baseline clinical variables between two study interventions. The pattern of missing data will be examined according to the procedure recommended by Little and Rubin [74]; which includes comparing group differences in the primary outcomes of subjects with versus without missing data. We will also test whether the drop-outs are random or systematic by comparing the drop-outs with the study completers on the baseline data. An absence of significant differences would support the random nature of drop-outs. Effect of drop-outs will be minimized by including all subjects in the analyses and by including any effect of systematic differences between the drop-outs and completers in the model as a covariate when applicable.

Each outcome variable will be graphed versus time for each subject for all available time points (baseline, mid-treatment, post-treatment, follow-up) to visualize the trajectory of change over time. The difference in the trajectory of change in outcome between two study interventions will be assessed by linear mixed effects models. The mixed effects method has several advantages over more traditional analytic approaches such as a change score, end-point, or repeated measures analysis of variance. It allows the inclusion of subjects with missing data or those who were terminated early in the study, without relying on data imputation procedures. This method considers the correlation between the repeated measurements within subjects, and it provides an estimate of the individual variability around the population trend. We will include fixed effects for intervention groups, time, and group-by-time interaction in the model; time will be treated as a categorical variable (baseline, mid-treatment, post-treatment, and follow-up). Both random intercept and random slope will be assessed. Model comparison will be performed using likelihood ratio test.

Baseline variables that are significantly associated with the outcome ($p < 0.15$) or significantly different between two study interventions ($p < 0.10$) will be included as covariates in the multivariable mixed effects model. A backward variable elimination will be used to remove insignificant covariates from the model. The variable with the largest p-value was removed from the model each and only variables with p-value$<$0.10 will be kept as covariates in the final model.

2.6.3. Multiple mediation models

Let Y denote the outcome CAPS change score, M_1, M_2 denote two mediators (Coping Model: tolerance of discomfort and coping), and X denote the intervention. To examine the sequential mediation effect of M_1 and M_2, we will fit three linear regression models.

1) $M_1 = a_0 + a_1X$;
2) $M_2 = b_0 + a_2X + b_{21}M_1$; and
3) $Y = c_0 + c_1X + b_1M_1 + b_2M_2$.

Three mediation effects will estimated from the above regression coefficients: the mediation effects from X which passes through M_1 only (a_1b_1), the mediation effect from X which passes through M_2 only (a_2b_2) and the mediation effect from X which passes through both M_1 and M_2 ($a_1b_{21}b_2$). The coefficient $c_1$is the estimated direct effect of X and the total effect of X is estimated by $a_1b_1 + a_2b_2 + a_1b_{21}b_2 + c_1$. A bootstrap technique will be used to calculate 95% confidence intervals for the mediation effects and the total effect. The mediation effect will also be quantified by calculating the proportion of the total effect explained by the specific mediation effect, respectively. The analysis will be conducted using R package *lavaan* [75].

2.6.4. Intervention modality

The primary analysis will include all randomized subjects. Because the intervention modality is modified due to COVID-19, we will adjust the analysis for study period. We will also examine whether modality modifies the effect of intervention on outcome; subgroup analyses will be performed for subjects with regular interventions and for subjects with virtual interventions as appropriate.

2.6.5. Missing assessments

Some of our mechanistic analyses will be impacted by our inability to conduct some assessments remotely. In particular, we will not be able to use a composite of attention measures for these individuals but will have to rely solely on the Digit Span Task. Similarly, the Mindful Breathing Task will not be used in conjunction with the PMS to quantify capacity to attend to the breath. Physiological data will not be available for remote participants, reducing our power for these analyses.

3. Discussion

The methodology of this trial was driven by the need for rigorous studies of mind-body interventions for PTSD and by the need to advance our understanding of the mechanisms by which such treatment may support change. We relied heavily on psychotherapy trials when developing the methodology (e.g., measures, timeline) for this study. This allows for greater comparability of outcomes to other non-pharmacologic interventions that are currently offered for PTSD. One important methodological departure, however, is the way in which we randomize participants. Specifically, we elected to use rolling individual randomization; in other words, eligible individuals receive their assignment immediately after baseline evaluation and are able to begin with the next available class. We hope that this strategy will maximize recruitment and retention as it eliminates the need to wait for a cohort to form, and we believe that it is justifiable because of important differences between therapy and exercise classes. There is no inherent order to the classes. The asana practice is the same each time to develop familiarity with basic yoga poses and body positioning. Teachers offer suggestions about the mental focus of the class (e.g., setting an intention, focusing attention, letting go of judgment), but these are "stand alone" as opposed to building on the prior week. Further, group discussion is minimal – like any community-based exercise class – so we are not concerned about fostering relationships among members.

A second difference from psychotherapy studies is our dissemination plan. Although Connected Warriors has a large national presence, we recognize that Veterans have multiple ways to access yoga, e.g., within VA facilities, in the community, online. It would be unrealistic to think that we could disseminate a particular practice or even assure that trauma-focused principles are followed in any class a Veteran might attend. Rather, our goal is to use what we learn to teach Veterans with PTSD how to become good consumers of yoga. One implication of this is that Veterans learn to attend to their internal experience and to have the knowledge and confidence to adapt poses that are not serving them well physically or emotionally. In doing this, it is important to differentiate between avoidance (i.e., not doing something based on fear of unwanted sensations that may arise) and self-care (i.e., preventing harm). Second, if our hypotheses about mechanisms of change are supported, it may be useful to develop PTSD practice guidelines to increase the likelihood of certain types of experiences. For example, if attentional control appears to have an important effect in mitigating PTSD, Veterans could be instructed to emphasize focus on the breath and the drishti (gaze) during yoga practice [67] or seek out poses that require heightened attention (e.g., balancing). Additionally, the approach could be recommended for Veterans with attention as a prominent clinical complaint. Similarly, if we find that affective reactivity and emotion regulation are mediators of the relationship between yoga and PTSD, we may guide Veterans to increase nonjudgmental awareness of internal sensations (e.g., noticing without judgment sensations that arise in different body parts during a challenging posture) and nonreactivity to discomfort (e.g., recognizing that one does not necessarily have to move if a posture is uncomfortable but not painful) during the yoga practice [67]. Mindfulness, which similarly involves an attitude of nonjudgment and nonreactivity, has been shown to impact emotion regulation strategies such as rumination and distraction [76] and may contribute to distress tolerance [77]. . Finally, practice characteristics could be modified to enhance beneficial physiological changes. Higher intensity movement and slow, rhythmic breathing may increase parasympathetic activity [67] and specific poses (e.g., inversions [65]; may foster these changes as well.

The COVID-19 pandemic provided an interesting opportunity for this trial. We did not originally plan to evaluate a distance modality but being able to offer yoga during social distancing mandates seemed like an important contribution to our local community. Schulz-Heik et al. [78] evaluated the feasibility and acceptability of telehealth ($n = 30$) vs. in-person ($n = 29$) participation in a clinical yoga program at a large VA medical center; Veterans reported similar levels of treatment satisfaction and acceptability across modalities, and there were no differences across groups in self-reported improvements in 16 physical and mental health domains (e.g., anxiety, depression, intrusive memories, sleep problems). Although we face the possibility that the data from those who participate remotely will not be combinable with data from in person delivery, at a minimum we will be able to further contribute to our understanding of the feasibility of utilizing online yoga as part of PTSD recovery, which may be especially valuable for rural Veterans or those for whom attending classes is logistically difficult.

Yoga is a highly popular practice, which is increasingly being leveraged as a part of Veterans' PTSD recovery programs. Although initial evidence suggests the usefulness of this strategy, the increasing number of people practicing yoga [6] adds urgency to understanding its efficacy for clinical applications for Veterans, including whether it can be differentiated from other types of exercise, and understand its mechanisms of action. Such information is critical if we are to find ways to replicably deliver yoga to Veterans for symptom management and understand who may confer most benefit from these types of interventions. By focusing on key mechanistic variables that are linked to the development and maintenance of PTSD and are impacted by yoga, we believe that we will be able to identify pathways to change. This information, in turn, can be used to optimize practice and create delivery guidelines. This study emphasizes cognitive mechanisms that drive mind-body interventions; future research should integrate this perspective with other potential pathways, including spirituality, behavior, physiology (e.g., HPA axis functioning), biology (e.g., GABA levels, immune functioning, epigenetics), and brain functioning and connectivity.

Declaration of competing interest

None.

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Abbreviations

ANT	Attentional Network Task
AUDIT-C	Alcohol Use Disorders Identification Test
BEAQ	Brief Experiential Avoidance Questionnaire
CAIR	Complementary Alternative and Integrative Research
CAPS-5	Clinician Administered PTSD Scale for DSM-5
COVID-19	Coronavirus Disease 2019
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
ERQ	Emotion Regulation Questionnaire
eStroop	Emotional Stroop task
ETRIP	Emory Treatment Resistance Interview for PTSD
CSR&D	VA Clinical Science Research and Development
DTS	Distress Tolerance Scale
HF	high frequency
HRV	heart rate variability
IRB	Institutional Review Board
ISI	Insomnia Severity Index
LEC	Life Events Checklist
LF	low frequency
MINI	Mini International Neuropsychiatric Interview
MoCA	Montreal Cognitive Assessment
PASAT	Paced Auditory Serial Addition Task
PCL-5	PTSD Checklist for DSM-5
PHQ-9	Patient Health Questionnaire
PMS	Philadelphia Mindfulness Scale

PTSD	Post-Traumatic Stress Disorder
RCT	Randomized Control Trial
RTSQ	Ruminative Thought Style Questionnaire
RYT	Registered Yoga Teacher
SDS	Sheehan Disability Scale
STAI	State-Trait Anxiety Inventory
STAXI-II	State-Trait Anger Expression Inventory – II
US	United States
VA	Veterans Affairs

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