Protocol for: Neurobiological Mediators of Self-Regulatory and Reward-Based Motivational Predictors of Exercise Maintenance in Chronic Pain and PTSD

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AIMS and HYPOTHESES

The assessment and treatment of chronic pain (CP) and Posttraumatic Stress Disorder (PTSD) are national priorities for the National Institute of Health (NIH) and the Veterans Health Administration (VHA) as we continue to see steep increases in the prevalence of these conditions among returning Veterans as well as relatively high rates of these conditions among civilians. Our laboratory has developed a rigorous, individually tailored, 3-month progressive exercise training program that appears to modify a key factor (neuropeptide Y: NPY) involved in the pathogenesis of CP and PTSD. Preliminary data suggest that progressive exercise-training induced changes in NPY system function were associated with improvements in PTSD, depression and pain-related interference and sensitivity, as well as intrinsic motivation to exercise. The proposed R21 will extend this research to examine the relationship between progressive exercise-training induced changes in NPY and the capacity for reward and self-regulation. These latter capacities are thought to be essential to intrinsic and extrinsic motivation and self-efficacy, which are known to promote long-term exercise maintenance, which is critical for long-term health maintenance. Findings from the study are therefore expected to inform development of more effective therapeutic interventions for CP/PTSD aimed at forestalling serious long-term disability and reliance on pharmacological interventions with high potential for abuse, dependence, and morbidity. In the proposed study, we will investigate the association between changes in key biological and neuropsychological factors induced by a rigorous, 3-month individually tailored, progressive exercise training program and achievement of exercise maintenance in a CP/PTSD population.

Aim 1. Evaluate whether changes in neuropeptide Y (NPY) system function correlate with changes in self-regulation and reward across the rigorous 3-month individually tailored, progressive exercise training program.
Hypothesis 1a: Pre-training resting plasma NPY levels will correlate with capacities for self-regulation and reward.
Hypothesis 1b: Changes in resting plasma NPY levels and the release of NPY in response to standardized cardiopulmonary exercise testing (CPX) conducted before and after a 3-month progressive exercise-training program will correlate with improvements in self-regulation and reward sensitivity.

Aim 2. Evaluate whether changes in NPY correlate with changes in self-efficacy and intrinsic motivation for exercise in response to a rigorous 3-month individually tailored, exercise-training program.
Hypothesis 2a: At baseline, acute exercise-induced increases in plasma NPY during CPX will correlate with exercise-related self-efficacy and intrinsic motivation to exercise.
Hypothesis 2b: The release of NPY during CPX will increase in response to the 3-month exercise-training program and correlate with increases in self-efficacy and intrinsic motivation to exercise.

Aim 3. Determine whether capacities for self-regulation and reward sensitivity, as well as self-efficacy and intrinsic motivation for exercise change in response to the 3-month exercise-training program and predict exercise maintenance.
Hypothesis 3: At endpoint, the factors under investigation will significantly predict exercise maintenance.

Aim 4. Evaluate whether changes in NPY system function across the 3-month exercise-training program correlate with improvements in pain sensitivity and interference, as well as depressive and PTSD symptoms.
Hypothesis 4a: At baseline, CPX-induced increases in plasma NPY will not correlate with pain-related interference and sensitivity, depression or PTSD severity.
Hypothesis 4b: At endpoint, CPX-induced increases in plasma NPY will correlate with reductions in pain-related interference and sensitivity, as well as with reductions in depression and PTSD symptoms.

Current effective treatments for CP/PTSD are limited. In addition, the treatment of CP and PTSD, which are commonly comorbid conditions, is typically undertaken by different clinical specialists working in separate specialty clinics. In contrast, this study is predicated on evidence suggesting that CP/PTSD comorbidity is mediated at least in part by common underlying pathophysiological factors. This study thus focuses on modification of one such biological factor that contributes to both CP and PTSD, and will provide valuable information about possible inter-related neurobiological and neuropsychological benefits of progressive exercise in veterans and civilians with CP/PTSD. This work may also serve as a foundation upon which innovative adjunctive treatments for CP/PTSD or other alternatives to current treatments for these disorders can be developed. For example, findings may lead to refinement of exercise behavior change protocols to fit the unique needs of this complex population and foster long term exercise maintenance. In addition, increased understanding of the neurobiological mechanisms of a successful exercise training intervention that leads to exercise maintenance may stimulate development of other epigenetic or pharmaceutical means of modifying biological factors key to the efficacy and maintenance of such treatments.

SIGNIFICANCE

The proposed R21 research study is aimed at developing an effective non-pharmacological, motivationally-based exercise training approach that can be maintained over the long-term to help individuals suffering from chronic pain and posttraumatic stress disorder (CP/PTSD) reduce and manage the symptoms of these highly comorbid disorders, as well as prevent related long-term negative health consequences and disability.

A. Development of a Non-Pharmacological Approach to Treating CP/PTSD

The National Institute of Health (NIH) and the Veterans Health Administration (VHA) has emphasized the importance of developing novel, non-pharmacological approaches to CP management. As many as one half to three quarters of patients who present for PTSD treatment have a significant CP condition.[1-4] Conversely, among persons presenting for treatment of CP, approximately 20% to 37% have PTSD.[5] In addition, substantial research suggests that the co-prevalence of CP and PTSD negatively impacts the course of both disorders, such that individuals who experience both conditions report greater pain, affective distress and disability than individuals with either CP or PTSD alone.[1-4]

Our laboratory has been examining the possible benefits of a rigorously defined, closely monitored individually tailored and motivationally based progressive exercise-training program for the CP/PTSD population. Such health behavior change paradigms are thought to be critical to improving CP in medically and psychiatrically complex populations,[6-8] as well as to reducing CP-related disability[9] and dependence on medications with high potential for abuse and morbidity, such as opioids.[10] However, although many researchers have successfully helped patients initiate regular exercise, establishment of exercise maintenance has been difficult to achieve in both general[11] and clinical[12] populations. The proposed R21 investigation is therefore designed to investigate the neurobiological and related neuropsychological mechanisms by which our 3-month progressive exercise-training paradigm may foster exercise maintenance.

As discussed below, brain and plasma levels of the anti-stress, anti-nociceptive neurobiological factor, neuropeptide Y (NPY) are reduced by exposure to extreme or chronic stress, and have been found to be low in both CP and PTSD. In our previous work, we showed that maximum load exercise testing can acutely increase plasma levels of NPY in patients with CP/PTSD.[13] Moreover, preliminary data from our current work suggest that the capacity to release NPY in response to maximum load exercise testing increases over the course of our 3-month, progressive exercise-training program in association with reductions in pain-related interference and sensitivity, as well as depression and PTSD. Moreover, the capacity for release of NPY in response to maximum load exercise testing was found to correlate with *exercise-related intrinsic motivation and self-efficacy, which have been previously shown to foster exercise maintenance.*

The proposed R21 is therefore designed to investigate hypothesized relationships between exercise-training associated augmentation of NPY system function and improved capacities for reward and self-regulation—neuropsychological capacities posited to underlie intrinsic motivation and self-efficacy, as well as predict long-term exercise maintenance.

B. Exercise-Training Induced Augmentation of NPY System Function May Mediate Benefits in CP/PTSD

Research in rodents and humans shows that severe chronic or life-threatening stress reduces baseline plasma and central nervous system NPY levels.[14-15] Effects of stress on NPY in humans and rodents are, however, individually variable. For example, exposure to extreme stress had minimal effect on NPY levels among “selected” Special Forces soldiers compared to “unselected” trainees over 3-4 weeks of selection training. In addition, NPY levels achieved at peak stress during survival training correlated negatively with dissociation and distress, and positively with military performance thought to rely on frontal lobe function.[16-17] In contrast, Vietnam Veterans with severe chronic PTSD had low resting plasma NPY levels and blunted NPY responses to sympathetic system activation.[18] Cerebrospinal fluid (CSF) NPY was also low in combat veterans with PTSD when compared to either healthy non-traumatized controls or combat-exposed healthy controls.[19-20] Of note, higher resting plasma NPY was associated with decreases in PTSD symptom severity retrospectively assessed over time, and with improvements in PTSD symptoms assessed across a wait-list controlled clinical trial whether or not the active PTSD treatment was received.[21-22]

Exposure to traumatic stress can lead to noradrenergic system hyperreactivity, which is the most replicated neurobiological finding across clinical studies of PTSD. As previously detailed,[23] norepinephrine (NE) released in the prefrontal cortex (PFC) at high levels during intense stress diminishes PFC-mediated working memory, executive function and inhibition of the amygdala.[24] NPY moderates the release of NE. Under conditions of low to moderate stress, resting levels of NPY *restrain* NE release from peripheral sympathetic neurons and in brain by activating NPY-Y_2 pre-synaptic receptors.[25] This moderates arousal and facilitates calmness. During high stress, NPY is released from sympathetic neurons and in brain; peripherally released NPY also crosses the blood brain barrier. In the brain, NPY counters the anxiogenic effects of corticotropin releasing hormone in the amygdala. In the periphery, NPY is rapidly metabolized to NPY_{3-36}, a selective NPY-Y_2 receptor agonist[26] that

returns the firing rate of sympathetic neurons and the release of NE back to baseline. Together these effects of NPY help maintain NE release in PFC within a range that optimizes PFC function. Thus PFC-mediated inhibitory control over the amygdala and defensive reflexes can be maintained, while planned behaviors can be implemented.

NPY also has pro-reward and anti-nociceptive properties.[27] For example, NPY prevents progression of acute pain to chronic pain, prevents opiate tolerance and withdrawal,[28] and directly enhances dopamine-mediated reward in the nucleus accumbens.[29-30] NPY is also anti-inflammatory, which too may enhance dopamine-mediated reward and reduce pain. As discussed in our review of the shared underlying neurobiology of CP and PTSD[27], pain contributes to amygdala reactivity, and activation of the amygdala to transmission of peripheral pain, as well as to potential impairments in frontal lobe executive function as outlined above.

In Summary, the capacity for NPY synthesis and/or release appears to be downregulated in PTSD and CP. We hypothesize that exercise training-induced augmentation of resting NPY levels and capacity for NPY release during stress will correlate with exercise-training induced changes in reward sensitivity, self-regulation, intrinsic motivation and self-efficacy for exercise—to thereby foster exercise maintenance.

C. Motivational factors related to Exercise Maintenance: Reward Sensitivity and Self-Regulation

The motivational aspect of our 3-month progressive exercise paradigm is based on both the Transtheoretical Model (TTM) of health behavior change and Self-Determination Theory (SDT) for exercise, which integrates well with the TTM stages of exercise behavior change and captures internal motivation to adopt and sustain exercise.[31] Importantly, SDT is based on theories of self-regulation and learning.[32] Thus, SDT supports our contention that capacities for *self-regulation and reward-based learning* will constitute neuropsychological manifestations of the effects of our 3-month training program on NPY system function and underlie motivation to sustain exercise. Our hypotheses are also supported by empirical evidence demonstrating that self-efficacy[33] and intrinsic motivational factors predict TTM-defined active stages of behavioral change, including exercise maintenance, in the general population.[34-35] This accords with recently published findings from our laboratory in a CP/PTSD population.[36] Among trauma-exposed women with fibromyalgia (73% with PTSD), there was a large effect size for higher levels of self-efficacy in the action and maintenance stages of exercise, even in the context of higher fibromyalgia-related interference. The means and standard deviations for self-efficacy in the non-active, pre-contemplative/preparatory vs. active stages of change were 38.64$\pm$7.15 vs. 51.4$\pm$9.45, respectively: $F(1,16)=2.02$, $p=.17$, $n^2= .11$. To our knowledge this is the first study to examine exercise-related self-efficacy and TTM stages of change for exercise in a trauma-exposed CP population. These findings support our current proposal and suggest that even with a high level of pain-related symptoms, patients with CP/PTSD who have or achieve a high degree of exercise self-efficacy will have an increased likelihood of sustaining exercise long-term.

Anhedonia, or loss of pleasure, is a transdiagnostic symptom of psychopathology observed in both depression and PTSD. Clinical neuroscience research into the mechanisms underlying anhedonia has drawn on a rich animal literature on the neural systems that support healthy reward processing[37-38]. This experimental animal research has elucidated two psychologically and neurobiologically distinct systems that support reward processing[39]. These include 1) *reward anticipation*, or interest in pursuing reward-relevant items or activities, which is mediated primarily by mesolimbic dopaminergic mechanisms; and 2) *reward consumption*, or the capacity for pleasure upon receiving a reward, which is supported by a neural network including prefrontal regions implicated in reward valuation, and 'hedonic hotspots' in the ventral striatum and brainstem. Clinical neuroscience research in humans suggests that both components are implicated in depression[40] and PTSD[41]. As such, the proposed project will examine exercise-training associated change in each of these components of reward sensitivity in relationship to changes NPY system function—as well as in relationship to change in symptoms of anhedonia, depression and PTSD, self-efficacy and intrinsic motivation to exercise, and exercise maintenance.

A recent meta-analysis[42] found more pronounced executive function deficits in PTSD patients compared to trauma-exposed controls. In addition, male gender, older age, war trauma, and higher severity of co-morbid depressive symptoms were related to poorer executive functioning among the trauma-exposed. For our study, we will utilize the Go/No-Go task to investigate the relationship between executive function as a measure of self-regulation and NPY system function. Slowed central processing of No-Go stimuli and more rapid responding to Go stimuli in a Go/No-Go task have been related to PTSD hyperarousal and re-experiencing symptoms.[43] PTSD patients also showed weaker activation of ventromedial (vm) PFC than trauma-exposed controls in the No-Go vs. Go condition; vmPFC activation, in turn, correlated negatively with fear-potentiated startle during safety signal learning and fear extinction.[44] Deficits in frontal lobe activation during performance

of this task by patients with PTSD also predicted poorer outcome in response to cognitive behavioral therapy.[45] Such studies thus support our hypothesis that baseline plasma NPY levels and release of NPY in response to exercise will correlate with response inhibition in this task—and that capacity for response inhibition will correlate with self efficacy, which in turn will contribute to the prediction of exercise maintenance.

D. Preliminary Data from our Individually Tailored, Progressive Exercise Training Program in CP/PTSD

While there have been numerous exercise-based studies for the CP population, meta-analyses reveal significant flaws in experimental design, and inadequate calibration and matching of exercise frequency, intensity and duration to CP type--resulting in mixed and unclear results.[37-38] There also have been few studies examining exercise as a treatment for PTSD[39]. Our standardized exercise testing paradigm and individualized training program were therefore developed to enable rigorous testing of the mechanisms and potential therapeutic effects of exercise in a CP/PTSD population**.** First we reviewed exercise studies in heart failure and cardiovascular disease populations, which share some pathophysiological characteristics with the CP/PTSD population.[46-47] Based on the Physical Treatment Model[48], individuals with CP are often sedentary and physically deconditioned and need a progressive approach to exercise training, as defined by the American College of Sports Medicine. Thus, in our ongoing study using such a paradigm**,** all participants completed an acute, symptom-limited, cardiopulmonary exercise stress test (CPX) before and after a 3-month supervised, progressive exercise-training program based on each participant's baseline fitness determined via the CPX.

Initial analysis of data from Dr. Scioli's active RR&D Career Development Award (CDA2) study using this training paradigm reveals that 4 participants [(3 CP/PTSD and 1 healthy trauma control (TC)] increased their capacity to release NPY in response to the CPX after 3 months of progressive exercise training by 23.8%, 59.9%, 76.9% and 100%. Two participants (1 CP/PTSD and 1 TC] showed no change in NPY responses. Among the CP/PTSD participants (n=5), there was a trend for a significant reduction in Clinician-Administered PTSD Scale (CAPS-5) scores between the baseline (M=32.2, SD=10.2) and endpoint assessments {M=15.6, SD=9.7) (p=0.10), yielding a Cohen's d of 1.67 (large effect size). Also, resting NPY levels (after exercise-training) correlated inversely with PTSD severity (r= -.61, p=.20).

Pain-related interference was clinically reduced between the baseline (M=4.4, SD=1.2) and endpoint (M=3.6, SD=1.3) (p=0.47) assessments, yielding a Cohen's d of .6 (medium effect size). Resting NPY before exercise training was weakly correlated with pain-related interference (r= -.36, p=.43), while resting NPY after exercise training was more strongly correlated (r= - .67, p=.15). Consistent with Dr. Scioli's previous findings,[13] peak NPY levels reached during CPX testing were positively correlated with pain threshold (r=.60, p=.20) after (but not before) exercise-training. In addition, the change between resting and peak NPY levels correlated strongly with pain threshold (r=.96, p<.001). Furthermore, the change in peak NPY reached during CPX testing after 3-months of exercise-training correlated with the change in pain tolerance (r=.64, p=.12).

Severity of depression measured by the Beck Depression Inventory (BDI-II) was reduced between the baseline (M=28.4, SD=15.4) and endpoint (M=17.0, SD=15.5) (p=0.05), yielding a Cohen's d of .73 (medium to large effect size). Resting NPY before training was not correlated with depression severity (r=.05, p=.91), but resting NPY after exercise-training was inversely correlated (r= -.61, p=.15).

Preliminary data also demonstrate a strong correlation between changes in the capacity for NPY release during the CPX (measured as the change from resting to peak CPX levels) across exercise-training and improvements in SDT-based intrinsic motivation (r=.96, p=008) and self-efficacy (r=.99, p-.014) for exercise.

Thus our preliminary results from this small sample trend in the direction of our hypotheses with effect sizes in the medium to large range.

E. Summary of Significance

(1) This study will establish whether exercise-induced changes in NPY system function are associated with changes in putative mechanisms that predict exercise maintenance—a problem that has dogged proponents of exercise as a health benefit for many years. If so, exercise programs can be calibrated to optimize/maintain changes in NPY system function, to more efficiently and effectively deliver immediate and long-term health benefits to patients with CP/PTSD and reduce health care costs.

(2) This non-pharmacological approach also could be used as an adjunct to existing cognitive-behavioral PTSD or pain therapies to enhance their efficacy—and potentially reduce progression to opiate use with the attendant risks of abuse, dependence, morbidity and death.

INNOVATION

(1) The proposed exercise paradigm represents a shift from general exercise prescriptions to a clinically feasible, rigorous individually tailored approach. Baseline CPX testing is used to inform the participant's exercise prescription based on heart rate range (HRR) rather than exercise type, thus controlling for exercise intensity. Data from our preliminary work and Pernow[49] show that the threshold for NPY release during exercise is strongly correlated with the anaerobic threshold and occurs at a *mean* of 75% of VO_2 max.

Progressively targeting individually determined HRRs to eventually reach the anaerobic threshold associated with NPY release will increase the likelihood that NPY synthesis and release will be upregulated across training. Using HRR as the exercise target also allows participants to choose their preferred exercise type (i.e. walking, running, cycling or swimming) and may increase the likelihood of long-term exercise maintenance. (2) Restoring or increasing the capacity to release NPY during stress through exercise is a novel PTSD and CP treatment approach, as well as a novel means to increase the likelihood of exercise maintenance via effects on capacities for reward and self-regulation.
(3) Integrating biological and neuropsychological constructs to improve therapies for the complex CP/PTSD population is novel and more likely to reduce disability and negative health consequences in the long-term.

APPROACH

Overall Strategy: The proposed research will assess effects of a rigorous, individually tailored 3-month progressive exercise training in patients with CP/PTSD on NPY system function during a standardized cardiopulmonary exercise test (CPX) as related to changes in pain sensitivity, depression and PTSD, reward sensitivity and self-regulation, and TTM motivational constructs related to exercise maintenance.
Participant Characteristics, Recruitment Strategies, Screening Evaluation: See Human Subjects section.
Scheduling of Women: Each cold pressor and CPX session in women will be scheduled 2-6 days after the start of menses during the early follicular phase (when estrogen and progesterone levels are low and stable), or after initiation of a new pill cycle in women on oral contraceptives. Women on other types of steroid contraception will be scheduled as convenient as steroid levels are generally constant.

Measures	**Eligibility** Screening Session	**Baseline** Resting CPT	**Baseline** CPX/CPT	**Midpoint** Resting CPT	**Post-Train** Resting CPT	**Post-Train** CPX/CPT	**F/UP 1 & 3 Month**
Baseline Dx Status							
SCID-5, LEC-5, CAPS-5	X						
BAT-L	X						
Pain Ratings							
WHYMPI- Interference	X		X	X		X	X
Numerical Rating Scale	X	X	X	X	X	X	X
Cold Pressor Test		X	X	X	X	X	
Psychiatric Symptoms							
BDI-II, PCL-5/CAPS-5	X		X	X		X	X
CSSRS	X			X		X	
Exercise Behavior							
TTM Stage Change	X		X	X		X	X
Exercise Motivation							
TTM Self-Efficacy/ SDT EMS	X		X	X		X	X
Executive Function & Self-Regulation							
Go/No-Go Task			X			X	
Generalized Self-Efficacy			X	X		X	X
Emotion Regulation Scale			X	X		X	X
Reward Sensitivity							
TEPS & EEfRT			X	X		X	X
Blood Biomarkers		X	X	X	X	X	

1. Structured Clinical Interview for DSM-5 (SCID)-5:[50] This current gold-standard clinician-administered interview will be used to diagnose psychiatric and substance abuse disorders except for PTSD (see below).
2. Life Events Checklist (LEC-5):[51] The LEC-5 will be used to code exposure to potential traumatic experiences and serve as a reference for the CAPS-5 assessment.
3. Clinician-Administered PTSD Scale-5 (CAPS-5):[52] This 30-item structured interview yields a dichotomous diagnosis of PTSD and a continuous score of severity for each symptom. The CAPS-5 is currently being validated, but the previous version CAPS-IV demonstrated excellent sensitivity (.81) and specificity (.95).[53]

4. VA Boston Assessment of Traumatic Brain Injury (BATL) Military and Civilian versions:[54] The BAT-L is the first validated semi-structured clinical interview to characterize head injuries due to blast or blunt neurotrauma and diagnose TBIs throughout the lifespan.
5. Beck Depression Inventory (BDI-II):[55] The BDI is a well-validated 21-item self-report measure of depressive symptom severity. It yields a total score and subscale scores for depressive cognitive and somatic symptoms.
6. PTSD Checklist (PCL-5):[56] The PCL is a 20-item self-report that assesses the extent to which an individual is bothered by each PTSD symptom during the past month using a 5-point Likert-type scale. The PCL-5 is undergoing validation, but the previous PCL based on DSM-IV had good sensitivity (.82) and specificity (.83).
7. Columbia Suicide Severity Rating Scale (CSSRS):[57] This validated scale is used routinely in clinical trials to assess historical and current risk for self/other harm.
Transtheoretical Model of Exercise Stage of Change:[58] This 23-item continuous measure categorizes stages of behavioral change (precontemplation, contemplation, preparation, action and maintenance).
8. Self-Efficacy for Exercise:[59] This 18 item scale is used to determine confidence in one's ability to exercise.
9. Exercise Motivation Scale:[60] This 31 item scale is used to determine extrinsic and intrinsic variants of exercise motivation based on Self-Determination Theory. Results from various analyses showed adequate evidence for the a priori hypothesized EMS factorial structure, acceptable subscale reliability estimates, and nomological validity.
10. Go/No-Go Task:[61-62] This computerized task measures response inhibition. Participants are asked to respond to certain ("go") stimuli and make no response "no-go" stimuli, while maintaining speed and accuracy The main dependent measure is the commission error rate (making a "go" response to "no-go" trials.
11. Generalized Self-Efficacy Scale:[63-65] This revised10-item scale taps into a global sense of self-efficacy, or belief by an individual in his or her ability (e.g., "I can always solve difficult problems if I try hard enough, " and "I can usually handle whatever comes [66-68] This 10-item self-report scale assesses habitual use of two common strategies to alter emotion captured on two sub-scales: cognitive reappraisal and expressive suppression. Items are rated on a 7-point Likert scale from 1 (strongly disagree) to 7 (strongly agree).
12. Temporal Experience of Pleasure Scale (TEPS):[69]This18-item self-report measure uses a Likert-like scale (1-6) to assess reward sensitivity. Two sub-scales with convergent and discriminant validity assess anticipatory and consummatory aspects of reward sensitivity.
13. Effort Expenditure for Rewards Task (EEfRT):[70-71]This computerized (Matlab) task (for which scripts have been obtained from the developer for study use) captures willingness to expend effort for rewards. EEfRT scores have been inversely related to anhedonia. The task has been validated in healthy college students[70] and adults with major depression and schizophrenia[71].
Cardiopulmonary Exercise Test (CPX): The symptom limited CPX test controls for confounders that potentially impact NPY. Participants will present to the VA Clinical Studies Unit (CSU) at 7:30 am after having fasted except for water after midnight. Urine toxicology and pregnancy testing, vital signs, and an EKG will be obtained, and a standardized 6 kcal/kg breakfast of carbohydrate/protein power bars will be provided. An IV then will be placed. The CPX is performed after two hours of rest and during which rating scales (see below) will be administered. The CPX test is performed per guidelines published by the American College of Cardiology.[72] During the CPX (performed on an upright bicycle), EKG tracing and intermittent BP readings, functional capacity (oxygen consumption or peak VO_2) and ventilatory anaerobic threshold (VAT) are measured to assess safety and fitness. Blood samples are obtained at -15 and 0 minutes before exercise and at each 3-minute increase in exercise load set by a standardized bike ramp protocol adjusted for age, bodyweight, and pre-test approximation of fitness. Rapid early adjustment of load based on the heart rate response (HRR) by the exercise physiologist allows all subjects to reach their maximum exercise load within comparable ~15 minute time frames. Achievement of peak VO_2 max is based on meeting 2 of 3 criteria: 1) respiratory exchange ratio >1.1; 2) plateau of VO_2 with increased load; 3) age-targeted heart rate achievement; 4) inability to continue pedaling. If, at any time, participants wish to terminate or are unable to perform the CPX, the session will be terminated after an appropriate and safe cool-down period. See Humans Subjects section for additional safety procedures employed to ensure participant safety.
Cold Pressor Test (CPT): Per standard CPT procedures,[73] participants will hold their right hand, up to the wrist, in a temperature controlled ice water bath, while keeping the hand still. They are instructed to say when they first experience pain and to withdraw their hand when the pain becomes intolerable. Pain threshold is defined as the number of seconds between hand immersion and the first report of "pain." Pain tolerance is defined as the number of seconds between hand immersion and hand withdrawal from the water. To prevent risk to subjects, a 7-minute time limit for immersion, unknown to the patient, is imposed. The CPT is performed just before and 30' after CPX testing to assess effects of acute exercise on pain sensitivity. To assess effects of exercise training on resting pain sensitivity, the CPT also will be performed 1-

2 days before each CPX and at the exercise-training midpoint. At these sessions, participants will engage in the same procedures (except the CPX) at the same time of day as those performed at the CPX sessions.
Progressive Exercise Training Program:[46-48] After the initial CPX and CPT sessions, participants return to the CSU for 2 exercise-training sessions with our exercise physiologist. A pre-programmed heart rate monitor that "beeps" when exercise intensity increases is provided to participants to ensure that the targeted HRR is reached in accordance with individualized progressive exercise prescriptions. After these sessions, the exercise physiologist will instruct participants to gradually increase the frequency of their prescribed exercise sessions at home (per protocol) to 3x/week by week 4. During weeks 4, 7, and 10 an investigator will call participants to check-in and discuss any barriers to exercise. Basic motivational interviewing techniques (i.e. reflective listening) and problem solving strategies (the current standard of care in this area) will be used to facilitate exercise compliance while maintaining safety. To verify home exercise, participants will wear an actigraph and heart rate monitor that measures activity and heart rate. Data from the heart rate monitor will be downloaded and reviewed with participants upon return to the clinic for test sessions.
Exercise Prescription: The exercise prescription entails a 10 minute warm-up and cool down at 30-50% HRR. The exercise portion lasts 30 minutes, initially at 40-60% HRR during weeks 1-2 followed by incremental increases in the HRR range by 10% every two weeks through week 6 (midpoint) when the exercise intensity is increased to 70-80% HRR and held there during weeks 7-12.
Exercise Training Follow-Up: Phone calls will be made at 1- and 3-months follow-up after completion of exercise training and testing. Ratings will be administered to determine whether exercise and improvements in symptoms and motivation have been sustained, as well as to identify barriers to continued exercise.

Statistical Analysis Plan
Power and Sample Size Considerations: Power calculations were carried out based on our recently published study[13] which measured NPY, at baseline and peak time-points, in response to a single cardiopulmonary exercise stress test (CPX). Achievement of a Cohen's d effect size of .5 will suggest statistically and clinically significant effects of the treatment within the CP/PTSD group. Thus, in order to obtain a power of 80% at the 5% level of significance a sample size of 30 participants will be required.
Data Analyses: Baseline demographics and descriptive variables (e.g., age, gender, pain duration) will be summarized. Descriptive summaries for continuous variables will be presented in terms of means and standard deviations while discrete variables will be summarized in terms of relative frequencies and percentages.
Aims 1-2 &4: The hypotheses under Aims1, 2 and 4 will be evaluated using unconditional latent growth models (LGMs).[74] The approach does not assume a linear trajectory and is thus ideal for this proposal. The intercept of the LGM will be centered on the baseline self-report data (i.e., first slope loading will be fixed to 0.0). The intermittent time point (midpoint) will be freely estimated, and the final post-training time point will have a corresponding slope factor loading fixed to 1.0. Accordingly, the mean and variance of the slope factor will convey the fixed (average) and random effects (individual differences) of change across exercise training. Effects of the exercise program will be evidenced by a significant slope factor mean (indicating significant change in the metric of interest). A significant slope variance will indicate individual differences in change across training and support further investigation of predictors of the variability.
Aim 3: At both CPX testing time-points, the putative mechanisms under investigation (reward, self-regulation, exercise-based SE and IM) will be correlated with each other using Pearson or Spearman correlations, as appropriate. Based on these findings, these putative psychological mechanisms will be entered as predictors in a discriminant function analysis to predict exercise maintenance.
Feasibility to achieve AIMS: Recruiting veterans can be challenging, but inclusion of non-veterans allows us to successfully carry out our studies in this area. To enhance recruitment, we both advertise and work with collaborators at affiliated institutions who refer participants. Finally, we have an experienced multidisciplinary team and infrastructure in place, which is critical to the success of our studies in this area. In Dr. Scioli's CDA2 study to date, there have been no dropouts once subjects begin exercise.
Additional Considerations: Some participants may not respond to exercise training which could spur the development of novel pharmacological approaches to address a possible inability to increase the release of NPY in response to exercise. We will collect and process additional blood at each session to enable measurement of additional relevant biomarkers of interest (e.g., neurosteroids, ACTH, inflammatory markers) as possible with additional funding by the NC-PTSD or other funding sources.

Protection of Human Subjects

8.1. Risk to Subjects

8.1a. Human Subjects Involvement and Characteristics

The study aims to consent and enroll ~90 participants (half male, half female) aged 18-60 in the screening evaluation in order to enroll 30 participants into the experimental study procedures (cardiopulmonary exercise testing, and training) over the full 2 years of the grant. Participants in the proposed research project will be include veterans and non-veterans, women and men who are between 18 and 65 years of age, of ethnic and racial backgrounds in proportion to those of the larger Boston community.

Inclusion/Exclusion Criteria

Participants will be included only after participation in the informed consent process and agreeing to the study procedures as approved by the Institutional Review Boards of both Boston University School of Medicine and VA Boston Healthcare System (where the study will be conducted). An IRB approved HIPAA waiver will be obtained in order to conduct telephone pre-screening of potential participants before scheduling them for in-person screening evaluations.

Participants with posttraumatic stress disorder (PTSD) and chronic pain (CP/PTSD) will be included in this study only if a medical history, physical examination, vital signs, EKG, and baseline laboratory studies including urine toxicology screens and a negative urine pregnancy test (woman only) indicate that symptom-limited cardiopulmonary exercise stress (CPX) testing will be safe. Women of child bearing capacity must agree to use effective contraception while participating; a urine pregnancy test performed on the morning prior to completing CPX testing will also be done.

Participants entering the study will be relatively sedentary, as defined by the American College of Sports Medicine (i.e., performing less than 30 minutes/day and less than 150 minutes per week of moderate physical activity). Participants must be free of medications and other substances (e.g., illicit drugs and alcohol) with effects that could hinder data interpretation for 2-6 weeks before the cold pressor test (CPT) and CPX testing depending on the medication and frequency of use (which must be cleared by the study Co-I and study MD, Dr. Rasmusson). Psychotropic medications are allowed, however, as long as the participant has been stable on them for three months. Those using tobacco will be included in the study and will not be required to lower or stop their dosage/intake; intensity of smoking will be monitored across the study via use of urine testing for cotinine (a long-lived metabolite of nicotine) at each test session. Regular morning nicotine users will be instructed to smoke/chew to satisfaction just prior to arriving at the Clinical Studies Unit for testing, which will be approximately 2-3 hours prior to performance of the CPT and CPX. If using pain medications other than opiates (which will not be allowed) participants must be off of them for 5 half-lives before CPT/CPX testing, generally about 24 hours.

Participants must have an ICD-9 diagnosis of chronic pain with a musculoskeletal etiology, as confirmed by the rehabilitation medicine doctor consulting to the study, and a confirmed comorbid psychiatric diagnosis of PTSD. More specifically, the CP/PTSD participant must meet for current chronic PTSD (≥3 months) as assessed by the CAPS-5, 1-Month Diagnostic Version. As we are interested in NPY system functional status as correlated with putative mechanisms that predict exercise maintenance (self-regulation, reward sensitivity, self-efficacy and intrinsic motivation for exercise), as well as exercise training related changes in clinical symptoms (pain-related interference and sensitivity, depression and PTSD severity), there will be no lower limit “cut-off score” for entry into the study, as long as DSM-5/CAPS-5 criteria are met. The literature suggests that there are relationships between PTSD severity and deficits in NPY. Therefore, in order to have optimum power to investigate *correlations* between NPY and these dependent variables, it is important to have the broadest possible range of NPY levels. Other anxiety or depressive disorders are permitted. Participants may be involved in supportive psychotherapies as long as their participation has been stable for 3 months prior to study entry and remains stable throughout the course of the study. Also, any participant with a mild TBI, grades I-III, as determined by the BAT-L, will be included. These rigorous criteria are being employed for safety reasons, as well as to allow valid and meaningful interpretation of the study results in this mechanism-focused study. These are procedures we already routinely use.

Participants will be excluded from participation in the study if they have a life threatening or acute physical illness (e.g., cancer), current schizophreniform illnesses (except for psychosis NOS due to PTSD

related sensory hallucinations), bipolar I disorder, or active suicidal or homicidal ideation or other risk to self or others requiring clinical intervention. Individuals with current or past alcohol and/or substance dependence (less than three months from date of screening assessment) will be excluded. Women who are pregnant or are planning to become pregnant within the next six months will also be excluded. Individuals seeking significant new pain treatment such as surgical interventions or who have a neuropathic origin to their pain will be excluded. Participants with chronic pain who cannot tolerate exercising in an upright bike and those who have had a clinical history of coronary artery disease or positive stress test, uncontrolled cardiac arrhythmia, a QTc greater than 500, moderate-to-severe aortic stenosis, > moderately severe arterial hypertension (systolic > 165 mmHg, diastolic >100 mm Hg) and more than first degree atrioventricular block also will be excluded from participation. Individuals with moderate to severe TBI, as evidenced on the the BATL, will not be included in the study and will be referred for appropriate care through the VA TBI center of excellence at VABHS or an appropriate VA or Boston community clinic. Finally, individuals taking chronic medications (e.g., medication for high blood pressure, high cholesterol, glucose intolerance or diabetes) will be excluded. As noted above, psychotropic medications will not be excluded due to their common usage in the CP/PTSD population.

8.1 b. Sources of Materials

All of the data for this project will be collected specifically for research purposes. Hard copy files will be kept in locked file cabinets within locked offices at VA Boston Healthcare Service (VABHS). Electronic data (e.g., digital audio-files of diagnostic interviews used for consensus diagnostic purposes) will be kept in a secure folder on a secured, password protected server, with access restricted to staff for this specific research study. Participant codes without personal identifiers will be assigned to each participant, and will be the only means by which collected data is labeled. The only list that will link the names of the participants with their participant codes will be kept in a secure, password-protected computer account on a separate drive from the research coded data and will be accessible only to IRB-approved members of the research team. Research team members associated with the VA MAVERIC biorepository where biological samples will be stored and non-VABHS research team members at outside laboratories where samples are processed will not have access to the link.

Four sources of data will be included in this project: (a) the initial telephone screen, (b) in-person screening evaluation comprised of questionnaires to obtain demographic information, self-rated symptom ratings, assessment of medical history and current physical health, and a psychiatric diagnostic interview, including an EKG, (c) exercise testing, and d) plasma neurobiological factor assays.

(a) Telephone screen: Participants will be invited to participate in a telephone screen to assess possible study eligibility and gauge interest. A file linking participant names and numbers described above will be stored on a secure, password-protected computer account on a separate drive from the research coded data and will be accessible only to the research team as previously noted. If potentially eligible and interested, the phone-screened individuals will be invited for an in-person screening evaluation.

(b) In-person screening evaluation: Demographics and self-report symptom questionnaires will be administered; the latter will provide information regarding trauma history and PTSD, depressive and other psychiatric symptoms. All information from these questionnaires will be identified with participant codes only. Structured diagnostic interviews will be completed by the study PI to confirm trauma history, PTSD diagnosis, risk to self/others, other psychopathology, substance use and ability as well as willingness to abstain from neuroactive substances or substances that might affect levels of the neurobiological factors to be assayed. All information from these interviews will be identified with participant code only. A Certificate of Confidentiality will be obtained from the NIMH to protect participants from potential legal demands for study data. Data from these interviews and questionnaires will be entered into the database and securely stored as noted above. Clinical interviews will be audio-recorded to determine diagnostic reliability only after obtaining appropriate consent. These digitized audio-recordings will be identified with participant codes only and stored on a secure folder on a secured server, with access restricted to approved staff, as described above. These audio-files, which may inadvertently divulge PHI (e.g. voice), will be stored on a separate server than the self-report, diagnostic interview, and other data without PHI. Potential medical issues requiring medical attention will be discussed by the PI with the study MD/Co-I, Dr. Rasmusson, as well as with the participant, and the participant will be referred to the participant's health provider as appropriate. Participants receiving

care outside of the VA will have to sign a consent for release of such information if direct communication between the research personnel and outside provider is desired.

(c) The symptom limited CPX sessions will be conducted in the VABHS Clinical Studies Unit (CSU) exercise physiology laboratory by qualified clinical- and research-credentialed staff. Participants will also perform exercise training sessions (per protocol) at the CSU with supervision by an exercise physiologist with available medical support should any safety issues arise. Data from these sessions (including actigraph and heart rate data) will be coded and stored using protections described above.

(d) Biological assays: Blood samples (on ice) will be processed immediately for plasma, which will be stored at -80^{C} in the VABHS MAVERIC biorepository. These samples will be labeled with a sample cose which is different than the participant's research code for other coded data. A list linking the participant research code and the biological sample code will be stored in a secured folder separate from the self-report and diagnostic interview data. These samples will be assayed off-site with IRB approval at a laboratory with which Dr. Rasmusson has a longstanding and reliable relationship. No identifying information will be included with the sample shipments, and the outside laboratory will NOT have access to information linking the sample codes to the subjects' other research codes or identifying information. At VABHS, tests for illicit drugs, cotinine and pregnancy tests are performed in the clinical laboratory and results are posted as required by VABHS policy in the research subject's clinical record on CPRS. This data, as well as that obtained from blood, urine and EKG testing at screening will be protected by a Certificate of Confidentiality. VA privacy rules also pertain to this clinical record. Potential active duty or reserve participants will be informed that the military has access to such files. All participants must consent to having a VA medical file created as part of their participation in the study. Lab results pertinent to research findings will also be added to the research database and stored on a password-protected secure server.

8.1 c. Potential Risks

Potential <u>medical</u> risks and discomforts to participants include:

1. Bruising, pain, fainting or infection from the blood draws may occur, although we take precautions to significantly reduce the risk of fainting (i.e. adequate hydration; participants lie flat during the blood drawing and IV placement, see below).
2. A range of discomforts and medical risks, including the rare risk of death, are related to symptom limited cardiopulmonary exercise testing (termed CPX for this proposal); see below.

Potential <u>psychological</u> risks to participants include:

1. Emotional discomfort during screening from discussing traumatic experiences and other mental health symptoms during diagnostic assessments.
2. Risk of harm to self/others
3. Potential delays in obtaining treatment: There would be expected to be delays in obtaining standard treatments for chronic pain and/or PTSD, including pharmacological treatments, during the participant's active participation in the study. For women, there may be a longer period of time (between 2 and 4 weeks) between when they are screened and when they begin the experimental procedures due to the need (scientifically) to perform the CPX testing during the follicular phase of the menstrual cycle.
4. Scheduling assessments and key sessions during specific menstrual cycle phases presents a moderate inconvenience.
5. Coercion
6. Potential breaches of confidentiality
7.

8.2 Adequacy of Protection from Risk

8.2a. Recruitment and Informed Consent

Recruitment: Participants will be recruited by posted advertisement (on bulletin boards, in print media, on the internet, on transportation routes and vehicles, by radio, per pamphlets distributed in healthcare facility clinics or gathering places for Veterans or individuals otherwise at increased risk of trauma such as domestic violence

shelters). Potentially interested participants will be instructed in the advertisement to phone the study recruiter and undergo an IRB-approved phone screen. During this phone call, the study and its procedures will be described in brief and participants will be informed of general study eligibility criteria. If it appears that the initial eligibility requirements are met, participants will be scheduled for an in-person screening appointment, during which the informed consent process and diagnostic assessments aimed to assess inclusion/exclusion criteria will be completed.

Informed consent: Individuals conducting the informed consent process will be trained by the PI and monitored over the course of the first several sessions to ensure adequacy of training. Prior to completing any study procedures, the participant will undergo the informed consent process. First the participants will be presented with a written explanation of the study and the associated risks and benefits to review. IRB-approved personnel administering consent will be available for spontaneous questions. Then, a member of the study team will verbally explain the purpose of the study and the risks and benefits associated with participation again. The participant will be given an opportunity and encouraged to ask questions and will be referred to the PI or study MD, as appropriate, to answer any questions about procedures or medical safety requirements. The participant will also be asked questions to ensure comprehension of the study procedures along with risks and benefits. The participant will be informed that he/she may take time to consider participating before signing the informed consent document, and can discontinue participation at any time without affecting availability of clinical treatment at VA or, of course, any community health providers. The participant will review and sign the consent form if he/she agrees to participate, and the form will be co-signed by the person obtaining consent. Each participant will receive a copy of the signed consent form and HIPAA authorization form for his/her records.

8.2 b Protection Against Risk

Medical:

1. *Blood drawing:* Bruising, pain or fainting from the blood draws may occur. We believe the likelihood and seriousness of this risk is low given steps we have in place to decrease these risks. Specifically, a VA phlebotomist from the clinical laboratory at VABHS or a trained research nurse (GCRU) or other trained and clinically credentialed personnel (e.g., MD) will draw blood using antiseptic procedures and butterfly needles. Blood drawing will be done with the individual sitting (or lying if needed) to minimize risk of fainting. We will also ensure that participants are well hydrated prior to blood drawing to increase the ease of the procedure.

2. Risks of CPX testing and exercise training sessions: These sessions are associated with a range of risks including possible death, although the latter risk is expected to be extremely small given the level of medical clearance required to engage in these procedures, the requirement that participants be medically healthy, specific test day precautions (urine testing to avoid possible risk of testing under the influence of illicit substances, good hydration), and medical precautions taken during the tests themselves (see below). In addition, there are possible discomforts associated with these exercise sessions. Although encouragement and careful medical supervision will help make these exercise sessions as agreeable as possible, some participants might still find them unpleasant.

   -Men may need to have parts of their chest hair shaved in order to attach electrodes for the continuous EKG recording; this hair grows back over the next few weeks.
   -Skin reactions to EKG electrode leads can occur and will be minimized by thorough cleaning of the electrode sites after the EKG.

-The breathing mouthpiece worn during CPX assessment may be uncomfortable. In addition, saliva tends to accumulate in the subject's mouth when the mouthpiece is in place. This may lead to drooling and discomfort until subject figures out how to swallow with the mouthpiece in place.
- CPX testing as conducted in this protocol is associated with a 1 in 10,000 chance of a bad reaction (heart attack or dying) in unselected populations. In populations that include persons referred for exercise testing because of cardiac symptoms, the risk of myocardial infarction or death from exercise testing is approximately 1 in 2500; the specific risk of death has been estimated at <0.01%. In an asymptomatic patient population, selected to have no history, signs, or symptoms of coronary artery disease *(as in this study),* the risk of harm would be expected to be even lower. To minimize such serious risks, an exercise physiologist trained in Advanced Cardiac Life Support (ACLS) will supervise the performance of MAX-EX testing to be sure that participants remain safe should any problems develop. Additional staff (nurse, PI, research assistant) also will be present and able to summon emergency help if necessary. The test is performed in the Clinical Studies Unit which affords immediate access to a code cart and defibrillator; in addition, an ACLS trained MD is stationed in the immediate area during testing, and a Code Blue Team can be summoned immediately.
-It should be pointed out that clinical cardiac stress tests and the experimental maximum load exercise test (CPX) described in this protocol are similarly stressful to the myocardium. The CPX test thus will be performed in accordance with guidelines published by the American College of Cardiology, but the criteria for stopping the tests will be more conservative for stopping than clinical cardiac stress testing. Both tests take participants to maximum "volitional" exercise load unless EKG changes, BP changes, or other symptoms suggest that the participant should end exercise testing prematurely. In terms of the EKG alone, such tests are stopped immediately if 1 mm of ST elevation or sustained V-tachycardia occurs. Recommended relative indications to stopping a test based on EKG changes include ST depression > 2 mm, arrhythmias such as multifocal PVCs, triplets of PVCs, supraventricular tachycardia, heart block, or bradycardia. We, however, use such “relative” indicators as clear indications to stop the test, and would then evaluate the participant and refer or transport as appropriate for treatment or further observation and re-evaluation. We also use 1mm instead of 2mm ST depression as an indication to stop the test and refer the participant for additional medical clearance by a cardiologist before allowing the participant to continue in the study.

Psychological risks:

1. *Emotional discomfort during screening:* The risks of discomfort from discussing traumatic experiences and other mental health symptoms during diagnostic assessments are moderate in both severity and likelihood. The assessor will let the participant know that the assessment can stop as needed until distress wanes; and the participant is informed that he/she does not have to discuss anything too uncomfortable for the participant. Clinical support or additional safety evaluations/management will be provided as indicated.
2. *Risk of harm to self/others:* Participants will be assessed for potential risk to self or others at each research clinic visit by the PI or study MD. In addition, a Columbia Suicide Severity Rating Scale (CSSRS) to assess history and immediate risk for self/other harm will be completed and immediately reviewed by a doctoral level, clinically credentialed researcher at screening and each clinic visit. Participants with active risk to self/others will be referred immediately for further clinical evaluation and treatment as appropriate, and against the participant’s will, if necessary, as outlined during the informed consent process. Potential participants *without* active risk to self/others, but with a history of a suicide attempt within 6 months of entering the study will not be eligible for entry into the study if being in the study delays entry into appropriate clinical treatment. Contact with the potential participant’s clinician will require a signed release of information form by the participant, as a pre-requisite to study participation, as described during informed consent.
3. *Potential delays in obtaining treatment:* There is expected to be a delay in obtaining clinical treatment for CP and/or PTSD, including pharmacological treatments, during participants’ active participation in the study. Emergency hotline phone numbers and other clinically relevant emergency numbers will be provided to participants to call during both office and out-of-office hours. For women, there may be a period of time (between 2 and 4 weeks) between when they are screened and when they begin the experimental procedures due to the need (scientifically) to perform the CPX sessions during the follicular phase of the menstrual cycle if cycling or using oral steroid contraceptives with varying steroid doses across time.

Emergency hotline phone numbers and other clinically relevant emergency numbers will be provided to participants to call during both office and out-of-office hours.

5. *Exercising at home:* We anticipate that the same risks during the exercise tests apply to the exercise prescriptions performed at home. However, in both the informed consent and through verbal discussion with each participant, we will encourage them to call 911 or go to the nearest emergency room for evaluation if they experience any chest pain or unusual shortness of breath or weakness while exercising at home. We also encourage participants to call the PI immediately if they experience any unusual, intense increase in their pain intensity levels during or after exercising, in order to be evaluated by the rehab medicine doctor so that he/she can provide a recommendation for modification of their exercise prescription as needed. Finally, we will also encourage all participants to call us if they experience any physical injury while exercising at home so they too can receive further evaluation by the rehab medicine doctor and modification of their exercise prescription and/or a referral for follow-up care by their primary care doctor (both inside and outside VABHS).

6. *Increase in Anxiety or PTSD Symptoms in Response to Exercise:* Some PTSD patients participating in exercise tests published by other investigators have reported an increase in intrusive thoughts or other re-experiencing symptoms or anxiety in response to exercise. Some patients with PTSD report that this can occur during or in response to everyday attempts to exercise as well. Subjects will be told that they can stop exercising or discontinue the study, if needed, if this occurs. In addition, the PI and Co-I, Dr. Rasmusson, the psychiatrist overseeing the exercise testing, will talk with the subject to determine whether any additional treatment should be offered to help with such symptoms. The subject will be instructed to call the Biostudies Unit during the day or the VA operator to get the psychiatrist on call after hours if an increase in PTSD or anxiety symptoms persists or occurs after the subject has left the VA. Finally, while participants are exercising at home, they will be encouraged to call the PI if they experience any increase in their psychological symptoms during or after exercising. The PI will then be able to determine if further intervention is needed.

7. *Potential coercion:* We expect that any risks of coercion will be low. First, participants who do not wish to participate in the study or who wish to drop out of the study after enrollment will not experience any negative consequences and will be referred to VA or community-based treatment for CP/PTSD if desired. Second, potential participants will initiate contact with study staff if they are interested, which reduces coercion. A potential human subjects concern is whether the financial compensation offered is too high and therefore coercive to participants. We believe the rate of compensation for the current study is fair and matched to time needed to complete procedures and any additional inconveniences. Travel is compensated to address a potential disincentive to study participation. Participants will be compensated for most study sessions based on the time required—as payment may be needed to offset babysitting costs or time away from work. We plan to pay at rates commensurate with time spent (~$20 an hour), which is the standard at VABHS. Specifically, participants will be compensated $90 for participation in the full screening evaluation, $50 for participation in each CPT session (3 total), $50 for participation in each CPX testing session (2 total), $25 for in clinic exercise training sessions (up to 10 total) and $10 for each home exercise session (26-31 total),$5.00 for each telephone call (during weeks 3 through 12 while he/she is exercising at home (up to 10 total)), and $20 for each follow-up phone call (1-month and 3-month). If the participant participates in all of the study procedures over the ~6 month study, he/she will be compensated up to $990.00. Finally, all study procedures will be fully explained during the informed consent process such that participants can make an informed decision regarding their level of commitment and willingness to engage in study procedures given the risks. In addition, participants will be informed and reminded that they are free to withdraw from the study at any point without forfeiting payment for any procedures in which they have already participated.

8. *Breaches of confidentiality:* As discussed above in detail, under the “Sources of Materials” section, many procedures have been put in place to decrease breaches of confidentiality (e.g., numeric coding of data without personal identifiers, limited access to lists that link research codes to identifiers, storage of study-related information in locked cabinets in locked rooms and/or on secure drives, use of a Certificate of Confidentiality, and institutional training, support and enforcement of privacy and confidentiality rules. Should a breach in confidentiality occur, the VA and BUSM IRBs, institutional officials in charge of the protection of the privacy, and the participant would be informed.

8.3 Potential Benefits of Research to Subjects and Others

The proposed study is consistent with VHA National Pain Management Strategy, which assures that all persons cared for in the VA healthcare system can reliably count on prompt and appropriate treatment of pain and psychological distress, as well as the intent of the President’s declaration that the opioid crisis in a

national emergency. The proposed study seeks to evaluate the efficacy of a potential treatment that may reduce suffering from comorbid CP and PTSD and improve quality of life and overall health, as well as potentially lower the risk for use/abuse/dependence on opiates.

In addition participants will learn valuable information about the understudied role of exercise in the potential treatment of co-morbid CP and PTSD. Information from the study also may help to inform the development and refinement of an individualized exercise treatment and a motivationally based exercise behavior change intervention to promote long-term exercise adherence, for individuals suffering from CP/ PTSD. Thus, there is considerable potential benefit for the proposed research to indirectly help research participants and others who also suffer from chronic pain and PTSD.

8.4 Importance of Knowledge to be Gained

Given the high prevalence of both CP and PTSD among Veterans and non-veterans, particularly the high co- prevalence of these two conditions, the current research is important in that it marks a first step toward a more psychologically and neurobiologically based look at the role exercise may play in the treatment for these conditions. More specifically, the proposed research will potentially identify exercise as one mechanism that may serve to moderate or mediate the shared factors that maintain the co-prevalence of these conditions. The delineation of the role of exercise will help to inform new treatment approaches for CP and PTSD. One such example is the potential for the development of an exercise behavior change protocol, rooted in the most evidenced-based motivational theories to date, that can either be integrated into existing cognitive-behavioral interventions or used as an adjunctive treatment by providers of other CP/PTSD treatments, thereby improving the efficacy of these interventions for this population.

8.5 Adherence to ClinicalTrials.gov Registration and Reporting Requirements

In adherence with federal requirements, the PIs will register the proposed clinical trial in ClinicalTrials.gov no later than 21 days after the first subject is enrolled. In addition, the reporting of summary results information (including adverse events) will occur no later than 1 year after the completion date; grant and progress report forms also will include a certification that all required submissions have been made to ClinicalTrials.gov.

Recruitment and Study Timeline

Activities CY 19	20	
Data collection: 30 completers (15 per year)		
Neurobiological assays		
Data analysis and manuscript preparation		

Data Safety and Monitoring Plan

As detailed above, participation in this protocol presents relatively modest to moderate risks to the participants. Should any serious adverse events occur, they will be reported within 48 hours to the VA Boston Healthcare System (VABHS) and Boston University School of Medicine IRBs. We will also report unanticipated adverse events (UAEs) to the VABHS and BUSM IRBs in accordance with each IRB's guideline. In addition, we will summarize all adverse events (cumulative and annual) in our annual requests for VABHS and BUSM IRB re- approvals. The PIs will regularly consider whether any adverse event affects the Risk/Benefit ratio of the study and determine whether modifications will be needed to the protocol procedures, risks section, or consent form (risks and inconveniences sections). We will assure the accuracy and integrity of the data by checking completeness of assessments prior to the ends of research visits; we will also check participant safety assessments (e.g., results of Columbia Suicide Severity Rating Scale, BDI-II, EKG results) before the participant leaves the research session to facilitate opportunities for further evaluation and treatment as needed. Data will be entered within a day of collection and verified within a week. These strategies will help reduce likelihood of missing or misrepresented data. In addition, we will

involve an independent medical monitor, not associated with the study, to review the study on a quarterly basis for adequacy of screen numbers, enrollment and completion of experimental procedures, number of UAEs and SAEs, and possible need to modify the study protocol. A report by the medical monitor will be generated for submission to the relevant study IRBs on an annual basis, as well as contingent with identification of systematic, significant and/or unexpected and/or serious trial risks.

Inclusion of Women and Minorities

Women and men will be recruited in equal numbers to the study. According to U.S. census data, 18% of Boston residents identify as Hispanic/Latino, 54% as Caucasian, 24% as African American, 0.4% as American Indian/Alaska Native, and 9% as Asian. Using only several of the recruitment strategies proposed in the current application, we were able to enroll 4% Hispanic/Latino, 43% Caucasian, 43% African American, 0% American Indian/Alaska Native, and 3% Asian in a recently completed similarly complex study conducted at VABHS. Because the demographic measure given in the previous study included ethnicity and race within the same question, we believe that the percentage of Hispanic/Latino participants was underreported. However, we will make concerted efforts to target Hispanic/Latino and Asian populations via recruitment at Boston Medical Center, which serves large urban minority populations. We will also target other methods (e.g., local flyering and advertising on subway lines) that serve neighborhoods that include greater proportions of individuals within these populations. Based on these recruitment efforts, past studies in our lab, and the current percentages of individuals of ethnic minority status in the Boston area, we anticipate that greater than 45% of our participants will be of minority status.

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