

Protocol
“Impact of Exercise Training on Pain and
Brain Function in Gulf War Veterans”

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Project sponsored by a grant from the
U.S. Department of Veterans Affairs

Project Summary

Musculoskeletal pain in soldiers who returned from the Persian Gulf War is a serious problem. Numerous studies have reported musculoskeletal pain as a primary symptom of sick Gulf Veterans (GVs), with ~100,000 Veterans (~15%) reporting unresolved pain affecting their social and professional lives (1). Pain and other symptoms are often disabling with 1 in 7 United States Veterans seeking care for war-related health concerns (2) and ~12% receiving disability compensation (3, 4). Thus, a significant number of military personnel are no longer able to perform their duties due to medically unexplained symptoms including pain, fatigue and cognitive problems. Importantly, recent evidence suggests that chronic pain complaints in most GV's have not resolved (5, 6). Similar problems appear to be on the horizon for Veterans from Operations Enduring and Iraqi Freedom (7, 8). Understanding the pathophysiological consequences of chronic muscle pain is important for better determining both the efficacy and mechanism of treatments aimed at decreasing debilitating symptoms and improving physical function among Veterans coping with chronic pain.

Given the dearth of experimental data in GV's with chronic musculoskeletal pain (CMP), we have patterned much of our research in GV's after our research in fibromyalgia (FM), a disorder with a primary symptom of muscle and joint pain in civilians. Our work (9-11) and the work of others (12) suggest that FM pain is produced and maintained by central nervous system (CNS) dysregulation of nociceptive and pain processes. Our work also suggests that phenomena similar to those observed in FM may be occurring in GV's with CMP. Like FM patients, GV's with CMP, 1) are more sensitive to experimental pain stimuli (13, 14), 2) exhibit exaggerated pain responses following acute exercise (13), 3) experience more muscle pain during acute exercise (14) and 4) show augmented brain responses to both painful and non-painful experimental stimuli. These data suggest that some of the same pathophysiological mechanisms involved in FM may be maintaining chronic widespread muscle pain in GV's. Critical unanswered questions include whether promising treatments for CMP in GV's can affect laboratory measures of pain sensitivity and pain regulation and whether these changes relate to clinical improvements. We intend to begin to answer these questions by examining perceptual and brain hemodynamic responses to standardized painful stimuli and documenting their relationships to clinical outcomes before, during and upon completion of a viable, novel treatment for CMP.

There are no known efficacious treatments for GV's suffering CMP. Efficacy studies are needed to begin determining effective treatments for our Veterans following their service of our country. In FM, exercise training (both aerobic and resistance modes) is widely recognized as one of the few consistently efficacious treatments, resulting in improved well-being, increased physical function and in some cases decreased pain (15). One large scale treatment trial of aerobic exercise in GV's with chronic multi-symptom illness showed only modest improvements in pain, fatigue and mental health (16). We believe this trial had several limitations that greatly attenuated the treatment's effectiveness; consequently, it is premature to discount exercise training as a treatment for GV's with CMP. Further, we propose a novel approach that employs progressive resistance exercise training (RET) to treat GV's with CMP, while obtaining objective measures of nociceptive function, brain white matter tract pathways and total physical activity.

In addition to exercise performed as part of a structured training program, physical activity behaviors are important determinants of physical and mental health. Greater total physical activity levels are associated with increased physical function, improved mental health, increased energy and decreased symptoms of chronic pain. To our knowledge, none of the exercise training trials in FM have actually measured the impact of the exercise training on physical activity behaviors during daytime hours outside the intervention. It is plausible that the adoption of a structured exercise training program reduces physical activities performed during the rest of the day, and that this change in total physical activity could affect health outcomes. Objective measurement of physical activity will allow us to determine whether RET increases, decreases or has no impact on total physical activity levels in GV's with CMP. This will allow us to begin to characterize sub-groups who benefit the most from RET (e.g. potentially those GV's that maintain or increase their extra-intervention physical activity). Thus, in addition to supervised RET, we will objectively measure total physical activity levels outside of the intervention using accelerometers before, during and following treatment.

In summary, we propose to determine the efficacy of RET for the treatment of CMP and associated symptoms in GV's. In addition, we will assess the influence of RET on total physical activity, pain sensitivity and regulation, and brain white matter tracts. By applying functional neuroimaging techniques in conjunction with pain psychophysics we will test how the brains of Veterans with CMP respond to sensory stimuli and whether these responses can be modified by exercise training. We plan to use blood oxygen level dependent (BOLD)

and diffusion tensor imaging (DTI) methods to evaluate the function of brain regions involved in pain processing and control and the microstructural properties of white matter tract pathways that connect these regions. In addition, we will determine the influence of RET on extra-intervention physical activity behaviors, testing a critical and unanswered question - whether total physical activity levels change as a result of engaging in a RET program in patients with CMP. The primary goals of this project will be accomplished by comparing GV's with CMP assigned to either RET or wait-list control (WLC) in a randomized controlled trial.

Background and Significance

The problem of musculoskeletal pain in Gulf War illness

More than 50,000 troops returned from the Persian Gulf reporting a myriad of medically unexplained symptoms with no identifiable etiology. Of those Veterans participating in the Gulf Health Registry, the fourth most frequently reported symptom is musculoskeletal pain (17). Clinical and factor analytic procedures established the presence of a chronic multi-symptom illness affecting Veterans following deployment to the Persian Gulf (18). Three categories of symptoms were formed: fatigue, mood-cognition and musculoskeletal pain. Predictive and confirmatory factor analysis verified musculoskeletal pain as one of the three major factors in GV's illnesses (18). Medical Outcome Survey (SF-36) data collected by the Iowa Persian Gulf Study Group (19) indicated that deployed symptomatic Iowa GV's exhibited diminished physical function including large amounts of bodily pain compared to non-deployed Veterans. Data estimating the prevalence of symptoms in 11,441 GV's versus 9,476 non-Gulf Veterans in the National Health Survey of Gulf-era Veterans and their families (1) indicated that twice as many GV's reported muscle (8% vs. 4%) and joint pain (15% vs. 8%) than non-Gulf Veterans. Based on these data, upward of 100,000 GV's (15% of 697,000) report unresolved painful complaints that significantly contribute to their functional impairment. It has been almost 20 years since the conclusion of the first Gulf War and epidemiological studies continue to indicate pain as a disabling problem for GV's (5, 6). Moreover, recent medical record data for soldiers from Operations Enduring Freedom and Iraqi Freedom indicate that CMP in the absence of an identifiable injury is likely to be a significant problem for Veterans of the most recent Gulf War (7). Data from medical care and disability estimates for soldiers returning from Iraq indicate that approximately 56% of possible diagnoses will consist of conditions involving diseases of the musculoskeletal and connective tissue (42%) and/or ill-defined conditions that are based on symptoms (17%) (8). This is a significant, enduring and costly illness that deserves attention.

Can resistance exercise training (RET) be an efficacious treatment for GV's with CMP?

There are no known efficacious treatments for sick GV's who were deployed to the Persian Gulf. In the absence of a clear etiology (e.g. chemical exposure, physical trauma), studies aimed at addressing symptoms and improving the quality of life of our Veterans are needed.

One consistently efficacious treatment for chronic musculoskeletal pain is exercise (20-22). Exercise training has been shown to result in improved physical function, decreased symptoms, increased feelings of energy and decreased feelings of depressed and anxious mood for a host of chronic pain conditions including peripheral arterial disease, widespread pain and fatigue, rheumatoid arthritis and fibromyalgia (21, 22). The most relevant comparison group for GV's with CMP is FM, a disorder with a primary symptom of widespread and medically unexplained muscle and joint pain, occurring predominantly in civilian women (23). In FM, a recent meta-analysis of aerobic exercise training found beneficial effects for physical function ($d = 0.66$ standard deviations), global well-being ($d = 0.49$), and pain ($d = 0.65$) (20). Only 3 RET interventions met criteria for inclusion in the review. Although the RET trials were rated as possessing low methodological quality, the results were promising showing large positive effects for global well-being ($d = 1.43$), depression ($d = 1.14$) and pain ($d = 1.68$) and a moderate positive effect on physical function ($d = 0.52$). Of the 1264 subjects assigned to exercise training, only five adverse events possibly related to exercise were reported and none were reported for strength training. One study noted that "...after the initial phase of training, the patients did not complain of any unusual exercise-induced pain or muscular soreness during the experimental period, and even intensive strength training did not worsen the symptoms". In contrast, exacerbation of symptoms was thought to have a negative impact on adherence, but was poorly tracked and reported. The authors concluded that aerobic exercise training produces important benefits for FM patients and that limited evidence suggests that strength training may have a greater effect on the patients' primary complaints of muscle pain. A recent

review of strength training studies found effects similar to those seen in aerobic training studies. Strength training was associated reductions in pain and fatigue, and improvements in cognition, self-esteem and depressed mood in adults with low back pain, osteoarthritis and FM (22).

Although exercise training is recognized as one of the few consistently safe and effective treatments in CMP, methodological rigor has been poor in many studies. Most studies have used aerobic exercise, with relatively few RET trials. Follow-up of patients and assessment of training volume (progression, intensity, frequency and duration) are also rare and incomplete. In fact, Busch et al. (2008) reported that when considering the intensity and duration of exercise tolerable by FM patients, “...*no study analyzed or reported these in a systematic manner.*” Further, exercise studies in FM have consisted of > 90% female samples, thus our understanding of the impact of exercise on widespread pain in males is limited.

We are aware of only one exercise training trial in GVs. Donta et al. (16) conducted a large scale treatment trial of aerobic exercise training and cognitive behavioral therapy (CBT) in GVs with chronic multisymptom illnesses including persistent pain, fatigue and cognitive complaints. For VA Cooperative Study #470, 1092 Veterans were randomly assigned to Exercise (n=269), CBT (n=286), Exercise plus CBT (n=266) or usual care (n=271). Exercise training consisted of one supervised laboratory session of low intensity exercise aerobic exercise per week for 12 weeks. The exercise prescription was intended to increase physical activity levels. Exercise intensity was determined by the participant and not reported. Veterans were encouraged to exercise an additional two to three times per week during the 12 week treatment trial, but adherence to this suggestion was not reported. For CBT, Veterans met in groups with a licensed therapist once per week for 60-90 minutes. Results indicated modest improvements for both exercise and CBT with respect to physical function (11.7 % and 18.5 %, respectively), but little improvement in pain. Secondary outcome improvements for exercise were found for fatigue, distress, cognitive symptoms and mental health. Adherence to exercise was poor with a median attendance of 6 exercise sessions over the 12 week trial and only 47% considered as treatment adherent. We believe that this trial had several limitations that greatly attenuated the treatment’s effectiveness. The primary limitations were: 1) an exercise prescription requiring only one supervised session, 2) use of a non-standardized exercise prescription not designed for progressive increases in intensity, frequency or duration, 3) failure to measure physical activity when the trial was designed to increase this behavior, and 4) poor adherence to both exercise and CBT conditions. Therefore, we believe that it is premature to discount exercise training as a treatment for GVs with CMP. In fact, it can be reasonably argued that exercise “training” did not occur in this large scale study with only 6 single bouts of exercise being attended. We also agree with the statements made by Hotopf (24) that, “*Despite the importance of large pragmatic trials, additional small trials of focused treatments in specialty settings are required to develop and assess appropriate treatments for GWVI.*”, and that it is useful “...*to establish whether a treatment can work under ideal conditions before attempting to determine whether it does work in the real world.*”

We intend to apply the lessons learned from both the FM and GV exercise trials and test the efficacy of RET for GVs with CMP. Specifically, we plan to test the impact of RET on pain, physical function and patient global impression of change (PGIC) in a well-defined group of GVs meeting criteria for widespread and chronic musculoskeletal pain. We will use a standardized exercise prescription that begins gradually to avoid symptom exacerbation, includes a planned progression designed to increase muscular strength and includes measures of total work to document progression and demonstrate a training effect. We will employ a recruitment and retention plan to help ensure adequate adherence to both RET and WLC conditions. We will collect detailed measures of symptoms, adherence and adverse events using validated questionnaires and standardized procedures. We will collect measures of total physical activity to determine whether RET increases decreases or does not change physical activity behaviors. Finally, we will begin to determine how exercise impacts CMP by exploring potential central nervous system mechanisms of chronic pain maintenance.

Does RET increase, decrease or have no effect on total physical activity in GVs with CMP?

Physical activity is an important determinant of both physical and mental health (*Physical Activity Guidelines for Americans*: <http://www.health.gov/paguidelines/committeereport.aspx>). Greater total physical activity levels are associated with increased physical function, improved mental health, increased energy and decreased symptoms of chronic pain (21, 25). To our knowledge, none of the exercise training trials of chronic musculoskeletal pain have objectively measured the impact of exercise training of total daily physical activity. In fact, few studies in the general population have examined this adequately (26). Using self-reports, studies in older adults have found no changes (27) in total physical activity with exercise interventions (28), while with

objective monitoring, obese children were found to decrease their total activity (29). More recently, a study of aerobic exercise training in adults using objective measurement of activity, and careful consideration of exercise vs. non-exercise activity found no difference in activity outside the intervention (30). It's possible that changes in low-level physical activity, or in other words, a simple reduction in sedentary behavior may have a meaningful influence on pain. The lack of objective measurement has precluded testing this hypothesis. It is plausible that for chronic pain patients the adoption of a structured exercise training program reduces physical activities performed during the rest of the day. In chronic fatigue syndrome (CFS), it has been hypothesized that patients have "activity limits" and that exceeding the limit may result in symptom exacerbation (31). In FM, sedentary behaviors have been attributed, in part, to the patients' fear that acute exercise will increase their painful symptoms (32); a stark contrast to the documented benefits of chronic exercise training. Therefore, we intend to objectively quantify daily physical activity of GVs with CMP using accelerometry methods. Objective measurement of physical activity will allow us to determine whether RET increases, decreases or has no impact on total physical activity levels in GVs with CMP and will allow us to begin to characterize who benefits from RET (e.g. possibly those GVs that maintain or increase their extra-intervention physical activity).

Can RET impact well-controlled laboratory tests of pain sensitivity & regulation in GVs with CMP?

Enhanced pain sensitivity and abnormal pain regulation to experimental pain stimuli are two of the most consistent experimental findings from studies of patients with FM. These and other data have provided evidence suggesting that CMP can be maintained by central dysregulation of pain processing. To date, the evidence in favor of the benefits of exercise for patients with CMP has been based largely on self-reported symptoms. Thus, the biological mechanisms underlying how exercise improves the symptoms associated with CMP have rarely been investigated. Studies examining objective outcomes of nociceptive processing are needed to determine the impact of exercise on CNS mechanisms of pain perception and regulation.

Pain sensitivity and pain regulation in persons with chronic pain.

Although there has been little experimental research directed at examining musculoskeletal pain in Gulf Veterans, like exercise training, insight can be gained from research that has been conducted in FM. In the absence of a clear peripheral pathology, FM researchers have turned their focus to the central nervous system (CNS). Specifically, tests of the nociceptive system suggest that FM pain is associated with abnormal CNS processing of sensory stimuli; also termed central nervous system dysregulation. Several different techniques have provided convergent evidence that increased pain sensitivity to experimental pain stimuli in FM is the result of augmented nociceptive processing and that this dysregulation may play a role in the maintenance of FM pain. Psychophysical experiments have shown that FM subjects exhibit a dysregulation of diffuse noxious inhibitory controls (33), an exaggerated wind-up response to repetitive pain stimuli (34) and an absence of an exercise-induced analgesic response (35). Data from our laboratory show that GVs with CMP also exhibit exaggerated sensitivity to experimental pain stimuli and become hypersensitive following acute exercise. To our knowledge, none of the chronic exercise treatment trials in FM have tested whether exercise training has an impact upon pain sensitivity or pain regulation of experimental pain stimuli.

Functional brain imaging of experimental pain.

Psychophysical pain assessment and functional brain imaging methods recently have been applied to understand the neural representation of pain in CMP. In a well-designed study, Gracely et al. (12) reported that fMRI brain responses to experimental pressure pain, set at either similar stimulus levels or similar subjective pain levels, were augmented in FM patients compared to controls. Regions of augmentation included the primary somatosensory cortex, inferior parietal lobe, anterior cingulate cortex (ACC), secondary somatosensory cortex, superior temporal gyrus and cerebellum. These data support the view that physiological processing of pain is altered in FM. They are consistent with results from our lab examining fMRI responses to heat pain in FM (9). These data support the hypothesis that CMP is maintained by augmented processing of nociceptive information (36, 37). Our preliminary neuroimaging data in GVs with CMP also support augmented brain responses to pain. For this project, we intend to test whether RET can impact neural responses to painful experimental stimuli.

Functional brain imaging of pain and the influence of attention and distraction.

Cognitive aspects of pain, such as anticipation and attention, are important determinants of the pain experience (38). Consistent with a multidimensional pain concept involving sensory, affective and behavioral dimensions, cognitions about pain can have profound impacts on the actions taken to relieve or cope with pain (39, 40). Further, anticipation, attention, avoidance and fear have all been shown to contribute to the experience of chronic pain and may, in part, determine whether acute pain develops into a chronic problem (41).

Pain requires attention. In healthy individuals, attention directed towards pain results in more intense pain perception, while distraction from pain results in decreased pain perception (42, 43). Heightened attention to painful symptoms is also associated with greater disability and health care utilization (44).

The effects of attention and distraction on BOLD responses to pain have been studied using a variety of experimental paradigms. Derbyshire and colleagues (45) using PET and the Stroop color-word task, reported two distinct areas in the ACC (mid- and perigenual cingulate) that responded to pain and the Stroop test independently. Similarly, Valet and colleagues (46), using the Stroop color-word task found evidence of top-down regulation of pain through a “cingulo-frontal” system where activity within the perigenual ACC and orbitofrontal cortex influenced activity within the periaqueductal gray (PAG) and thalamus.

Cognitive modulation of pain appears to have both excitatory and inhibitory characteristics. Using a distracting maze task and the cold pressor pain test, Petrovic et al. (47) reported that distraction from pain resulted in increased activity in frontal cognitive regions (orbitofrontal and ventromedial prefrontal cortices) and decreases in “somatosensory association” areas (secondary somatosensory cortex and insular cortex). Attention to cognitive tasks results in decreased activity in areas involved in pain perception (insular cortex and mid ACC) and increased activity in regions involved in attention and cognition (i.e., orbitofrontal and perigenual ACC)(42). The PAG has also been shown to increase during cognitive tasks but only when combined with painful stimuli (48).

Our preliminary data suggest that changes in pain during distraction are significantly related to PAG activity in controls but not FM patients and that FM patients require greater distraction than controls to regulate their pain response. Treatments that improve pain symptoms may also improve the patients’ ability to attend to cognitive tasks. The weight of evidence from randomized controlled trials indicates that exercise training improves executive function, including better attentional control, among older adults (49). For this project, we will test whether RET can impact pain modulation in GV with CMP by delivering painful stimuli during a distracting cognitive task. If RET is beneficial, we would expect that the Veterans’ ability to distract from pain would be enhanced and the neural responses to pain will reflect this by showing increases in regions associated with pain modulation and decreases in areas associated with pain encoding.

Can RET impact pain-relevant brain white matter tracts in GV with CMP?

Diffusion tensor imaging technology is just beginning to be applied to the study of pain and the nociceptive system. Work detailing the ability to acutely image white matter tract trajectories from select thalamic subnuclei (50) shows promise for applying these methods to CMP populations where white matter tract abnormalities may be contributing to the maintenance of chronic pain. White matter tract abnormalities have been demonstrated for migraine patients (51). A recent study in FM suggests that DTI is particularly useful for understanding potential mechanisms of CMP. Sundgren et al. (52) reported that FM patients exhibited significantly decreased fractional anisotropy (FA) values in the right thalamus compared to healthy controls and that FA values within FM were significantly and negatively correlated with ratings of clinical pain and perceived pain control. Research in healthy subjects has demonstrated the utility of DTI methods for assessing potential nociceptive systems. Hadjipavlou and colleagues (53) showed that DTI could be used to demonstrate white matter tract connections between cortical and sub-cortical structures involved in pain control (i.e. prefrontal cortex, amygdala, thalamus, hypothalamus and rostroventral medial medulla) and both the PAG and nucleus cuneiformis; regions central to descending inhibitory and facilitory control, respectively. The sensitivity of DTI for tracking illness and recovery, and the relationship to disease outcomes, has recently been documented for traumatic brain injury (54) and schizophrenia (55). These studies demonstrate this methods potential clinical utility.

We will use established DTI methods to characterize white matter tract microstructure and trajectories along pain-relevant tracts originating from the thalamus, PAG, IC, orbitofrontal and perigenual cingulate cortices. These regions have been shown to interact in the top-down cognitive control of pain (16) and our

preliminary data in FM patients suggest that several of these regions do not respond normally during distraction from pain. DTI data will provide structural information on the integrity of white matter tracts to support our functional brain data. If RET is beneficial, we would expect changes in DTI parameters that would be suggestive of improved white matter structure. This would be represented by increases in fractional anisotropy and/or decreases in mean diffusivity. Dr. Alexander's lab has developed advanced DTI analysis methods including tractography algorithms for determining white matter structure and connections, including those involving the thalamus and frontal lobes (56-58).

Significance

The goals of this project are directly relevant to the VA mission that "...places a high priority on research aimed at improving the quality of life for Veterans of the 1990-1991 Gulf War affected by chronic multi-symptom illnesses..." (April 27, 2006, statement by the Under Secretary for Health, Dept. of Veterans Affairs (Jonathan B. Perlin) to the Senate Committee on Veterans Affairs). The goals are also consistent with recommendations by the Research Advisory Committee on Gulf War Veterans' Illnesses (59) calling for an expansion of "...research efforts that utilize state-of-the-art neuroimaging technology to better characterize differences between ill Gulf War Veterans and comparison groups." The application of physical activity measurement, psychophysical testing and neuroimaging methods in the context of RET treatment trial is a potentially powerful approach for determining the efficacy of exercise as a treatment for CMP symptoms, as well as, abnormalities in nociceptive processing. For example, our preliminary data showing that GV's with CMP have enhanced neural responses to pain suggests that treatment strategies should focus on correcting this CNS abnormality. Therefore, this proposal will provide valuable information on neural processing of pain and its' relationship to clinically meaningful outcomes.

Relevance to Veterans Health

Musculoskeletal pain in soldiers returned from service in the Persian Gulf War represents an understudied phenomenon that greatly adds to suffering and disability of the men and women who serve our country. These symptoms are difficult to deal with and the lack of knowledge pertaining to pathophysiology has left military physicians poorly equipped to treat symptomatic soldiers (3). Numerous studies have reported musculoskeletal pain as a primary and disabling symptom for GV's. While descriptive data based on self-report are important for highlighting problems, it sheds little light on etiology nor does it suggest treatments. Studies aimed at determining efficacious treatments while testing potential mechanisms of CMP need to be conducted to help treat presently sick Veterans and to help avoid active duty soldiers from entering the downward spiral to disability that accompanies war-related illnesses. Although this research directly tests the influence of RET on pain and physical function, there are numerous health benefits of being active. As detailed in the 2008 physical activity guidelines (<http://www.health.gov/paguidelines/Report/Default.aspx>), regular physical activity is associated with reduced risk for all-cause mortality, coronary heart disease, stroke, hypertension, colon cancer, type 2 diabetes, improved well-being and reduced symptoms of mental health disorders. Therefore, exercise is an important potential treatment with many positive benefits to the Veteran, and few drawbacks.

Specific Aims and Hypotheses

Aim 1: To determine the influence of RET on valid measures of pain (0-100mm visual analogue scale (VAS)), physical function (Physical Component Summary (PCS) of the short-form (SF-36) and patient global impression of change (PGIC) in GV's with CMP compared to WLC. The primary outcome will focus on whether RET results in *clinically meaningful differences*. Secondary outcomes will assess other aspects of pain and mental health of potential importance to the quality of life of GV's including qualitative descriptions of pain, pain coping styles, sleep patterns, self-esteem, symptoms of fatigue, anxiety and depression.

Hypothesis 1: GV's with CMP assigned to RET will show statistically significant and clinically meaningful improvements in self-reported pain, physical function and PGIC compared to WLC. We also expect significant improvements in the secondary outcomes known to change after exercise training (e.g. sleep, self-esteem, fatigue, anxiety and depression).

Aim2: To determine the influence of RET on total daily physical activity levels using complementary subjective self report and objective measures (accelerometers).

Hypothesis 2: GV's with CMP assigned to RET will show an increase in total physical activity by the end of the trial that is attributable entirely to an increase in RET.

Aim 3: To determine the influence of RET on brain mechanisms of pain **sensitivity** and **regulation** in GV's with CMP compared to WLC. Brain responses to painful heat stimuli will be measured using fMRI. Pain sensitivity will be determined by exposing participants to mild, moderate and strong pain stimuli. Pain regulation will be determined by having the participants perform attention-demanding cognitive tasks while receiving moderately painful stimuli.

Hypothesis 3A (Pain Sensitivity): GV's assigned to RET will show decreased ratings and decreased brain responses to experimental pain stimuli by the end of the treatment trial compared to baseline.

Hypothesis 3B (Pain Regulation): By the end of the treatment trial, GV's assigned to RET will show **decreased** brain responses in areas that process the sensory aspects of pain (e.g. cingulate & sensory cortices), and **increased** brain responses in areas that modulate or inhibit pain when diverting their attention away from a painful stimulus compared to baseline.

Aim 4: To determine the influence of RET on pain-relevant brain white matter tracts in GV's with CMP compared to WLC by conducting DTI analyses of white matter tracts from the thalamus to regions of the brain involved in pain processing and control (e.g. insula, periaqueductal gray, frontal and cingulate regions).

Hypothesis 4A: GV's assigned to RET will show improvements in white matter (measured as increased fractional anisotropy and/or decreased mean diffusivity) compared to baseline.

Research Design and Methods

Pilot subjects:

Five healthy adults (ages 18-60) will be recruited for a single MRI scanning session.

Screening and exclusion criteria for pilot subjects:

Once they are enrolled, pilot subjects will be screened during a face-to-face interview with a member of the study staff. Pilot participants will be screened to ensure that they are not color-blind, claustrophobic, or have metal in their body. Female pilot subjects who are pregnant, planning on becoming pregnant, or who cannot confirm they are not pregnant will not be eligible. Pregnancy status will be obtained at two levels of our experimental procedures. First, we will ask that they read and sign a statement at the end of the consent document confirming that they are not pregnant. Second, our MRI technicians will ask all female subjects to confirm that they are not pregnant prior to entering the scanner for each scan.

Subjects:

Sixty-eight U.S. military veterans of the Gulf War (1990-1992) with chronic musculoskeletal pain (**ages 35-65 yrs**) will be recruited and randomly assigned in blocks (to ensure 34 participants in each group) using the Research Randomizer tool (randomizer.org) to 16 weeks of RET or WLC.

Screening and exclusion criteria:

All participants will be initially screened by phone and asked to provide a letter from their physician approving their participation in a RET program. Primary eligibility criteria are 1) deployment to the Persian Gulf (e.g., Iraq, Kuwait, Saudi Arabia) for the purpose of Operation Desert Shield or Operation Desert Storm during the first Gulf War (1990-1992) and 2) current chronic widespread pain in multiple quadrants of the body lasting for at least 3 months. Veterans who regularly engaged in resistance exercise will not be eligible for study participation. Participants will be screened to ensure that they are not color-blind or claustrophobic, have no metal in the body and are not disabled to the point where RET would not be possible (e.g. wheel-chair bound). The Waisman Laboratory MRI center has a standard safety screen that all patients and research subjects must complete prior to entry into the 3-Tesla environment. Participants will be further screened to ensure that they are not taking any anti-convulsant or certain analgesic (e.g. opioids, muscle relaxants) medications for at least three weeks prior to the study. They will also be screened for the presence of other exclusionary criteria including explained pain conditions such as arthritis and injury, major depressive disorder with melancholic features, substance abuse or dependence (within 2 years), schizophrenia, bipolar disorder, medical or neurological disorders, peripheral neuropathy's and skin rashes on the areas that are to be pain tested.

Participants will also be assessed for the presence of FM, using American College of Rheumatology criteria (23). We will not exclude for the presence of FM, and if a significant number of GVs with unexplained pain screen positive, FM will be used as a covariate in our statistical model.

All participants will receive a clinical assessment in a private exam room at the Madison VA. The clinical assessment will be conducted under the supervision of Dr. Alan Bridges (MD, Rheumatology, Chief of Staff, Madison VA) by a member of the study staff trained by Dr. Bridges to collect a brief medical history and conduct a basic rheumatological exam. This assessment will occur on Day 1 of the protocol and will include a general physical examination, FM assessment and a chart review for verification of the exclusionary conditions and medications listed above. These procedures will ensure that GVs with CMP meet case criteria for widespread pain, do not have an explained chronic pain condition (e.g. rheumatoid arthritis), and that issues of substance use and abuse are handled prior to experimental testing. In addition to VA Human Subjects Training, all study personnel responsible for conducting the clinical assessment will complete the VA privacy and information security training (i.e., Information Security 201 for Research and Development Personnel & VA Privacy and Information Security Awareness and Rules of Behavior) and will be cleared by the Madison VA for access to the VA Computerized Patient Records System (CPRS). Subjects will be reminded prior to each experimental testing session not to consume coffee or other food or drinks containing caffeine for at least 4 hours prior to testing, not to smoke or use tobacco or nicotine products for at least 4 hours prior to testing, not to consume alcohol, and not to take any additional medications such as aspirin or other non-steroidal anti-inflammatory medications, cold medicine or antihistamines for at least 24 hours prior to psychophysical and brain imaging tests.

Axis I psychiatric status will be assessed with a clinical interview using the Mini International Neuropsychiatric Interview (MINI). The MINI is a brief, structured neuropsychiatric interview developed to assess major Axis I psychiatric disorders in DSM-IV and ICD-10, and is a screening instrument that is consistently used in studies conducted at the Madison VA. The reliability and validity of the MINI have been confirmed in previous studies (60). Dr. Lickel will supervise the screening of all Veterans (see letter-of-support) and his Research Nurse, or a member of the study staff trained in administration of the MINI, will administer the MINI to Veterans who meet initial eligibility criteria based on our phone screen. Veterans who screen positive for major psychiatric disorders will be offered referral to the VA Mental Health Services (Dr. Lickel, Chief of Staff, Mental Health Line).

Subject Identification and Recruitment

Recruitment will focus on the Madison commuting area primarily served by the Madison Veterans hospital. Dr. Alan Bridges, Chief-of-Staff for the William S. Middleton Memorial Veterans Hospital in Madison will oversee the recruitment process in collaboration with Drs. Cook, Lickel and the study coordinator. Our lab has completed one VA-funded study of Gulf War Veterans living in the Madison area (#H-2006-0050), and a second VA-funded study on GVs with CMP is underway with veterans in the VISN-12 region (#H-2008-0193). Veterans will also be recruited from participants of these projects via a mailed letter. The letter will be mailed only those individuals who requested that they be notified of future studies and the purpose of the letter is simply to make them aware of our efforts to recruit for the current protocol.

Our primary recruitment strategy will be to mail a letter announcing the study and the opportunity to volunteer to Veterans in the Madison VA or VA Great Lakes Health Care System (VISN 12) patient databases meeting our age (35-65 yrs) and deployment criteria (Persian Gulf, 1990-19921). The database searches conducted for the purpose of mailing the recruitment letter will only request name and mailing address. No additional personal health information will be requested as part of either of these searches. The search of the VISN 12 database will be conducted locally by Madison VA staff under the supervision of Dr. Bridges. The VISN 12 database search will require the approval of the VISN 12 Network Director among others and will not be conducted until we have received **all** necessary approvals. The recruitment letter to be mailed to patients will be reviewed and approved by Dr. Bridges and will go out under his signature. Similar to the database searches described above, we also plan to submit a request to the Post Deployment Health Services (PHDS) Gulf War Registry administrated by Dr. Aaron Schneiderman (Department of Veterans Affairs, Office of Public Health, Post Deployment Health, Epidemiology Program, Washington, District of Columbia). We will be requesting names and mailing addresses for Veterans in the Gulf War Registry living within 100 miles of the

Madison VA and meeting our age and deployment criteria for the purpose of mailing them our recruitment letter in order to make them aware of our study. To best protect the confidentiality of prospective subjects, we will work with the Privacy and Information Security Officers at the Madison VA and their counterparts at the releasing VAMC to complete a Data Use Agreement (DUA; VHA Handbook 1080.01). No sharing of data between the two institutions will occur until the DUA has been reviewed and approved by **all** necessary parties. Once the DUA has been approved, we will submit a copy of the final version for supplemental approval by the UW HS IRB and Madison VA RDC. We will abide by all provisions of the agreement in the transfer of the generated mailing list to the Madison VA. The electronic file containing the list will be encrypted, password-protected and securely maintained within the Madison VA Network firewall on the desktop computer in Room G2 of the Madison VA Hospital. Only the PI and study staff members whose duties include subject recruitment and retention will have access to these files. The mailing list generated from the search of the PHDS Gulf War Registry will be destroyed (i.e., deleted) in accordance with VA and VHA policy and as stipulated in the DUA following the closure of enrollment for the current project.

We plan to advertise via flyers in the various VA and hospital clinics in the area. Paper versions of the flyers will be posted on facility bulletin boards and digital versions of the flyers will be displayed on video monitors or digital bulletin boards. In addition, we plan to contact administrators at local Veteran and non-Veteran hospitals and clinics and request that they send out an informational email message to medical personnel employed at their facilities in order to make them aware of the study.

At the state level, we are coordinating with numerous Veteran Service Organizations (VSO) to reach Veterans who may not access VA health services. These include: 1) State public affairs offices, 2) Wisconsin Disabled American Veterans, 3) the American Legion, 4) Wisconsin Veterans of Foreign Wars, and 5) the National Gulf War Resource Center. We plan to distribute paper and digital flyers to representatives of these organizations for the purpose of sharing them with their members. Based on the success of the previously described recruitment efforts we may place advertisements in local or national periodicals (e.g., newspapers, magazines) and post study announcements, with permission, on VSO websites. We also plan to purchase advertising space on local public transportation (e.g., buses) and outdoor billboards in and around the Madison metro area in order to post a version of our study advertisement.

We will use evidence- and theory- (cognitive behavior modification) based strategies to optimize participation in both the RET and WLC conditions (61). Multiple strategies will be used as they are more effective than a single strategy approach (62). For RET we will contact by phone anyone who misses a workout to provide social support for continuing their exercise program. We will offer flexible hours and weekends to allow the Veterans choices of the best day and time for their work out. For both the RET and WLC groups, plenty of parking is available and transportation will be reimbursed up to \$750. We will also keep in close contact with our participants and remind them through cards and phone calls of their appointments. We will also distribute small exercise related prizes (t-shirts, exercise balls, etc.) as a way to provide incentive for training session attendance and completion of symptom questionnaires. For those subjects assigned to the resistance exercise condition, we will tally the training session attendance at the end of the first 4 weeks of training and award an incentive to those subjects who attended at least 80% of their scheduled twice-weekly training sessions. For those subjects assigned to the WLC condition, we will tally the completed symptom questionnaires (at least 50% of items have been answered) and award an incentive to those subjects who have completed at least 80% of their weekly symptoms questionnaires. The same procedures will be followed at the second, third and fourth 4 weeks of the 16-week study session. The monetary value for each of these incentive items will be between \$5-10. The incentives will be printed with a promotional logo which will hopefully aid recruitment for the study. The logo will include the lab phone number and email address in order to facilitate current or past subjects sharing lab contact information with prospective participants. Participants will be reimbursed for travel expenses at the standard VA rate up to a maximum reimbursement of \$750. Participants will also receive \$75 for each testing session (\$525 for attending all 7 testing sessions). For those who finish the 16 week trial (RET and WLC) and complete $\geq 80\%$ of scheduled exercise/testing sessions we will award them a \$300 payment towards a gym membership in their local area. In addition, WLC participants who complete $\geq 80\%$ of scheduled testing sessions will be offered 16 weeks of free personal training with our exercise specialists at the VA hospital in Madison and a \$300 payment towards a gym membership in their local area. All Veterans will be informed of these incentives prior to the beginning of the program and periodic reminders will be used as encouragement.

Study Schedule

This study will take approximately 6 years to complete. Due to unanticipated delays we did not make our originally projected start date of (January 1, 2011). Thus study procedures, including recruiting and the review of patient records for that purpose, were not initiated until January, 2013. We plan on testing 6 cohorts under each condition and individual cohorts will be involved in the study for 16 months. We anticipate completing the last training session in approximately 3.5 years and concluding the last follow-up in approximately 4.5 years.

Subjects will be recruited by direct contact, letter, peer referral, or advertisement and will be screened over the phone prior to written consent and the first day of testing. A confirmation letter and packet that contains introductory study information will be mailed to individuals who meet eligibility criteria based on the phone screener. Informational packet will include a copy of the consent form, a description of fMRI, and a map and driving directions to the Madison VA. Individuals who are eligible will also be invited to attend an informational session at the VA hospital. Attendance at the session is not mandatory for participation. The informational session is designed to provide potential subjects with information regarding study participation and reduce subject attrition following enrollment. During this session project staff will cover: 1) study design, 2) time commitment for participation, 3) time-line for participation, 4) description of the RET training program, 5) subject responsibilities (i.e. attend sessions as scheduled) and 6) subject compensation as detailed in the consent form. Subjects will have an opportunity to read through the consent form (signing of consent form will not occur at this time) and ask any questions they might have. Subjects will also have the opportunity to schedule their baseline testing session. Scheduling can also be completed over the phone at a later date. Potential subjects who attend the informational session and are not interested in participating will not be contacted further regarding this study.

Following enrollment, subjects will be asked to undergo five phases of testing that will include: 1) a clinical interview and a clinical assessment at the Madison VA hospital; 2) psychophysical and cognitive testing in a mock MRI environment; 3) repeated psychophysical, cognitive, and physical activity assessments as well as functional neuroimaging, which will overlap with; 4) a 16-week resistance training exercise (RET) regimen or wait-list control (WLC) depending on group assignment; and 5) follow-up with test sessions at 6 and 12 months after the completion of primary testing. The clinical interview will occur following written consent and will be completed on the first day of testing in a private office at the VA hospital. A clinical assessment will also occur in a private exam room at the Madison VA following written consent to ensure study eligibility. Upon completion of the clinical interview and assessment, testing will commence and will consist of filling out questionnaires, participating in psychophysical and cognitive performance testing and undergoing MRI environment habituation in a mock MRI. After completing the initial test day and confirming the Veteran's eligibility to continue participation they will be assigned to their condition, either RET or WLC, and scheduled for the baseline MRI scan. We plan to test in cohorts of 12 Veterans, 6 in each condition, by screening individuals over a 1-2 month period and conducting baseline scans for all cohort members over a 2-week period. The RET regimen and WLC will begin the week following the baseline scan and continue for 16-weeks. Veterans in both conditions will make 3 lab visits during the course of the RET/WLC with a fourth lab visit after the 16-week intervention has concluded. Two follow-up lab visits will take place at 6 and 12 months after the completion of the primary testing. A bulleted version of the study schedule appears below:

◆ Pilot testing

- We plan to enroll enough pilot subjects to test the exercise and brain scanning procedures on 5 individuals. Pilot subjects will be asked to complete a modified version of the brain scanning procedures which will include the administration of painful stimuli, cognitive task and perceptual rating.
- Pilot subjects will be recruited by an email message addressed to the faculty, staff and students in the Department of Kinesiology at the UW-Madison. They will read and sign pilot subject-specific informed consent and HIPAA authorization forms for their unique research involvement.
- Pilot subjects will be informed of all procedures and asked to read and sign a pilot-specific informed consent.
- They will be made aware that their willingness to participate as a pilot participant will not affect any relationship with the PI and that their decision to participate or not participate in the pilot sessions will in no way impact their grades, performance evaluations, or progress in the Department of Kinesiology

- They will then complete the Waisman MRI screen in order to ensure they can safely enter the scanner environment.
- Pilot subjects will be asked to submit to an identical scanning procedure as the full protocol subjects with the exception that they will be asked to refrain from rating a proportion of the thermal stimuli to which they are exposed.
- ◆ **Subject recruitment:**
 - Letters announcing the study and the opportunity to volunteer will be mailed to Veterans who have previously participated in studies in our lab (#H-2006-0050, #H-2008-0193) and indicated an interest in being notified of future studies.
 - Following a review of the Madison VA and VA Great Lakes Health Care System patient databases, letters will also be sent to select individuals from these databases meeting basic study requirements. The letters will be approved and signed by Dr. Alan Bridges (Chief of Staff, VA Madison; see letter of support from Dr. Bridges).
 - Local advertisement via paper and digital flyers placed in the community and in local and VA rheumatology clinics.
 - Paper and digital flyers distributed to local veteran and patient groups (e.g., Veterans of Foreign Wars).
 - Advertising purchased from local or national periodicals (e.g., newspapers, magazines).
 - Advertising purchased from local public transportation entities (e.g., Madison Metro)
 - Posting of study on websites <http://www.clinicaltrials.gov> and <http://www.centerwatch.com>.
 - Posting of study on VSO websites.
 - Printing a study logo on incentive items to be awarded to current subjects.
 - Potential subjects will be recruited by their individual response to our advertisements, letters, or a peer referral. Inquiries would be answered in the order in which they are received.
- ◆ **Brief Phone Screen:**
 - Interested participants will undergo a brief (10-15 min) screening interview over the phone to determine potential eligibility for study participation.
 - The phone screen will not collect sensitive data (e.g. illicit drug use), but will include information concerning exclusions for the study.
 - Eligible subjects willing to participate will be scheduled for their initial day of testing.
- ◆ **Informational Session**
 - Participants will be invited to participate in a non-mandatory information session after completion of initial phone screening
 - Study description, participation time-line, and compensation will be discussed
 - Participant questions will be addressed
 - Participants will have the opportunity to schedule their baseline testing session
- ◆ **Day 1 of Testing**
 - **Informed consent:**
 - Written informed consent will be obtained for all study participants prior to the collection of any research data. We will ensure that all participants understand the procedures of the study and what is expected of them based on their future experimental group assignment. Specifically, all subjects will be informed that they will be asked to undergo a clinical interview at the VA to fully determine study eligibility and that this interview collects sensitive and potentially stigmatizing data. Subjects will also be informed about the nature of the psychophysical, cognitive and fMRI testing as well as the RET/WLC regimen.
 - **Clinical Assessment (physical examination, completed immediately after consent):**
 - Following informed consent, subjects will have their disease status confirmed by the VA rheumatology clinic under the direction of Dr. Bridges. Authorized study personnel, trained by Dr.

Bridges, will conduct a general physical examination, FM assessment and a chart review for verification of exclusionary medications and conditions.

- **Structured Clinical Interview (to occur immediately after physical exam):**
 - The clinical interview will be conducted by a member of the study staff trained in the administration of the MINI under the supervision of Dr. James Lickel (Chief of Staff, Mental Health Service Line) to definitively determine the subjects' eligibility for the study.
 - The instrument used will be the Mini International Neuropsychiatric Interview (MINI). This is the standard instrument for the VA.
- **Psychophysical, cognitive and mock MRI testing**
 - The first day of testing will occur in the MRI simulator room at the Waisman Laboratory for Brain Imaging and Behavior.
 - Psychophysical pain testing will occur during this session, both before and during the MRI simulation procedure.
 - The cognitive task will be introduced and subjects will be permitted to practice the task. This same task will be employed during the MRI simulation as well as actual scans.
- **Physical Activity Assessments**
 - During the week prior to Day 2 participants will wear an activity monitor which will record intensity and frequency of physical activity
- **Participants are assigned to their experimental condition, either RET or WLC**
 - Participants assigned to the RET group will work with study staff to schedule their training sessions for the 16-week trial.
 - Participants assigned to the WLC group will be instructed to maintain their current level of physical activity and exercise for the 16-week trial.

◆ **Day 2 of Testing**

- **Baseline psychophysical, cognitive and functional brain imaging (to occur within 2 months of the first day of testing)**
 - fMRI data collection during psychophysical pain testing and cognitive performance tasks will occur in the 3T MRI room at the Waisman Laboratory for Brain Imaging and Behavior.

◆ **16-Week Trial (will start approximately 1 week after Day 2)**

- **RET group members will attend twice-weekly training sessions (90 minutes) with a personal trainer at the VA Physical Therapy clinic**
- **Outside of test days, WLC group members will go about their typical daily routine**
- **Both groups will complete a small battery of clinical symptom questionnaires on a weekly basis either at home (WLC) or just prior to a training session (RET)**

◆ **Blood Sampling**

- **RET group members will have blood samples drawn one hour before and thirty minutes following their first training session of the week during weeks 2, 7, and 15.**
 - Total volume of blood drawn over the duration of the study for participants in the RET group will be 240 ml.
- **All blood draws will be conducted by a certified phlebotomist who is also a member of the study staff.**
- **Blood draws will take place in the Exercise Psychology Laboratory at the University of Wisconsin-Madison.**

◆ **Days 3, 4 and 5 of Testing**

- **Psychophysical, cognitive and functional brain imaging data will be collected at weeks 6 and 11 of the 16-week trial and one week after completion (week 17)**
 - fMRI data collection during psychophysical pain testing and cognitive performance tasks will occur in the 3T MRI room at the Waisman Laboratory for Brain Imaging and Behavior.
- **Physical Activity Assessments**
 - During the week prior to Days 3, 4 and 5, participants will wear an activity monitor which will record intensity and frequency of physical activity

◆ **Follow-up Testing**

- ***Psychophysical, cognitive and functional brain imaging data will be collected at 6 and 12 months after completion of 16-week trial***
 - fMRI data collection during psychophysical pain testing and cognitive performance tasks will occur in the 3T MRI room at the Waisman Laboratory for Brain Imaging and Behavior.
- ***Physical Activity Assessments***
 - During the week prior follow-up testing participants will wear an activity monitor which will record intensity and frequency of physical activity

Summary of Experimental Design

This protocol is a randomized controlled trial of RET in GV with CMP. The overall goal of the trial is determine whether RET is an efficacious treatment for GV with CMP. Our primary aims and hypotheses are based on baseline compared to end of treatment responses. However, we have designed our trial to address some of the temporal aspects of the behavioral response by measuring our dependent variables at several points during and following RET and WLC. We feel that this is a critical aspect of the design that will provide valuable data to inform future investigations. Clinical symptoms and brain activity and anatomy will be evaluated throughout the trial to assess changes across time. The WLC group has been employed in order to gauge the impact of resistance training when compared to no treatment in GV with CMP.

For the purpose of psychophysical pain testing, all heat stimuli will be applied to the skin of the hand and forearm using Medoc thermal sensory analyzer (TSA) devices with a 900mm² Peltier thermode (Medoc Advanced Medical Systems, Ramat Yishai, Israel). The Medoc TSA devices are thermal sensory and pain stimulators designed for use in clinical and research settings. Use of these devices for research purposes has been permitted by the FDA and they have been used in research settings around the world without serious incident. These devices have also been previously approved by the IRB for use in our lab (#H-2005-0288, #H-2006-0050, #H-2007-0289, #H-2008-0193, #H-2010-0144) and used without incident. The principal investigator has used devices of this type for more than 15 years on patients with various chronic pain conditions in both MRI and behavioral settings without incident. We will assess warm and pain sensitivity across a range of temperatures (35 to 49°C).

The Stroop color word task will be used to assess cognitive performance and to divert attention. It is a sustained attention task that presents the words “red”, “green”, “yellow” and “blue” in the colors red, green, yellow and blue. The words are presented in either congruent (the word “red” appears in the color red) or incongruent (the word “red” appears in the color blue) fashion. Subjects are asked to name, as quickly as possible, the color and ignore the word. Testing will be conducted in both the simulated and actual MRI settings.

Day 1 (Screening Day)

Clinical and psychiatric assessments will be conducted after informed consent is obtained and prior to random group assignment. Following the clinical and psychiatric evaluation, qualified Veterans will be taken to the Waisman Center for Brain Imaging and Behavior to undergo: 1) testing on the primary outcome measures for Aims 1 and 2, 2) initial psychophysical pain testing, 3) MRI habituation, and 4) instruction for use and provision of an accelerometer for baseline physical activity assessment.

The primary outcome measures to test efficacy are visual analogue scales (VAS) of pain intensity and affect of widespread muscle pain symptoms, the physical component summary (PCS) of the SF-36, and the patient global impression of change (PGIC) scale. These valid measures are widely used and recommended as core outcomes in chronic pain treatment trials (63). The primary outcome measures for Aim 2 are self-report and objectively measured estimates of total physical activity. Self-reported physical activity will be measured using the International Physical Activity Questionnaire (IPAQ). Objective estimates of physical activity will be obtained using an accelerometer during the week immediately preceding the baseline visit to the Waisman brain imaging laboratory, at weeks 5, 10 and 16 of RET or WLC and at 6- and 12-month follow-ups.

Suprathreshold pain sensitivity will be assessed using scaling procedures as described by Gracely and colleagues (64). For painful heat stimuli, subjects will be randomly presented one of three stimuli (45°C, 47°C,

or 49°C) using the Medoc TSA described above. Each temperature will be presented randomly thrice for a total of 9 stimulus presentations, with an inter-stimulus interval of 1 min. Each subject will receive one block of stimuli to the thenar eminence of the left hand during initial sensitivity testing and then be exposed to a second block of 'moderate' stimuli during the Stroop/Pain run of the MRI simulation. Baseline temperature will be set at 32°C. The temperature will increase at a rate of 40°C per sec until the desired temperature for that particular stimulus is achieved. The target temperature will be sustained for 20 sec and then decreased at a rate of 40°C per sec. Painful heat will be rated on two separate category-ratio scales (64). One scale will assess intensity and the other unpleasantness. Each scale contains 12 verbal descriptors aligned to numeric ratings ranging from 0 to 20. Subjects will rate the intensity and unpleasantness immediately following each temperature. Category-ratio pain scales have established validity and reliability for assessing experimental pain stimuli and provide data necessary to create psychophysical curve estimates (65). The pain intensity ratings from the randomly presented stimuli will be used to establish each participant's individual temperature used to elicit the moderate pain ratings during fMRI scanning. The three absolute thermal stimuli (45°C, 47°C, and 49°C) will be used throughout the trial and pain ratings to them will serve as the primary outcome variable for pain sensitivity. The total number of 20-second thermal stimuli for the simulation will not exceed 18. In the interest of comfort and safety, at least one member of the study staff will be with the subject in the MRI simulator room at all times. Subjects will be informed that if at any time during testing they feel they can no longer tolerate the stimulus, they should verbally indicate as much and we will immediately halt the stimulation procedure and remove the thermode from their hand. The Medoc TSA devices are equipped with an emergency stop on the front panel of the unit. In addition, any stimulation procedure in progress can be immediately interrupted with a keyboard shortcut (hitting the "S" key) on the laptop which runs the TSA software. In the event that a stimulation procedure is interrupted, either by use of the emergency stop or keyboard shortcut, the face of the thermode will revert to the default baseline temperature, 32°C.

Our experience and data in CMP patients show that MRI habituation procedures are effective to screen for claustrophobia, deliver relative pain stimuli, enhance task performance and minimize subject motion. MRI habituation will take place in the MRI simulator at Waisman. This will entail being placed in a mock MRI unit, trained to rate painful stimuli, and perform the cognitive tasks (Stroop) using the same equipment that will be used in the 3T MRI unit. Pain psychophysics are also conducted and used to calculate the temperature designed to elicit moderate pain ratings. We have found that by habituating subjects they report feeling more at-ease in the MRI which should enhance measurement reliability. Our motion parameters indicate that by habituating subjects' data loss due to motion artifact is limited. In our FM study, quality data analyses indicate that only 6 of 100 subjects had motion exceeding 3 mm. The mock MRI is virtually identical to the actual MRI including fed-in scanner noise. Subjects practice with a scanner-compatible button-press response unit (Current Designs Inc., PA) while viewing stimuli through MRI compatible goggles.

Physical Activity Assessment

Baseline physical activity assessment will occur for one week prior to baseline brain imaging using an accelerometer. Physical activity will also be assessed for one week prior to each testing session. Subjects will be given instructions on the proper use of the accelerometer and will be asked to wear it as much as possible, unless sleeping, bathing or swimming, for the week preceding their baseline assessment.

Baseline Assessment and 16-Week Trial (RET vs. WLC)

After the baseline physical activity assessment, Veterans will return for baseline brain imaging including tests of pain sensitivity and regulation and diffusion tensor imaging. As a safety precaution for pain testing during the MRI scan, all subjects will be provided with easy access to a squeeze-bulb alarm in order to interrupt a scan in progress. Subjects will be instructed to use (squeeze) the alarm trigger if they can no longer tolerate the pain stimulus or if they are too uncomfortable in the scanner to continue. Standard procedure for the MRI technicians at the Waisman lab is to immediately stop the scan if the subject triggers the alarm. Likewise, study staff will immediately stop any thermal stimulus protocol in operation should the subject trigger the alarm. If the procedures during a scanning session are interrupted due to an equipment failure, we will end the session and ask the participant to reschedule. Subjects will be paid \$75 and have travel reimbursed for any session ended prematurely for any reason.

Once the first twelve Veterans are screened, baseline tested and assigned to groups we will begin the first 16 weeks of RET and WLC. During RET and WLC protocols, Veterans will be scheduled to return to the Waisman center on weeks 6, 11 and 17 for retesting of the primary and secondary outcomes. The testing will be conducted on the non-exercise training days or prior to exercise on training days to avoid having acute exercise influence the outcomes. Physical activity assessment via accelerometry will always be collected on the week immediately preceding visit to Waisman (i.e. weeks 5, 10 and 16) so that we can determine the relationships between total physical activity, symptoms and brain function and structure. Due to the number of brain scans required, and the availability of the 3T MRI, we plan to test Veterans in small cohorts on the same day. However, should a particular participant fall out of time with their respective cohort, we will test them per the protocol (i.e. at 6, 11 and 17 weeks). During each 16-week cohort, we will be screening, clinically assessing and baseline testing the next cohort of 12 Veterans to begin their 16-week assignment. Veterans will be tested at 6 and 12 months post RET or WLC in order to obtain follow-up symptom, physical activity and brain function and structure data.

Blood Collection

Blood will be collected and processed using the standard procedures of the Pharmacogenomics Analysis Laboratory (PAL) located at the Central Arkansas Veterans Healthcare System, Little Rock, AR by a certified phlebotomist who is also a member of the study staff. Briefly, blood will be drawn from the participant's arm into four 10 ml EDTA tubes. These tubes will be balanced and then centrifuged at 3300 RPMs for a total of 12 minutes within 7 minutes of collection. After spinning, the white blood cell layer will be isolated and drawn off into 5 ml tubes. These tubes will be placed in disruption buffer containing RNAase-out RNA-Later, vortexed to lyse the cells, coded and then quick-frozen in liquid nitrogen and stored in a -80 °C freezer until they are shipped for processing and analysis (blinded) at PAL. Blood draws will take place in the Exercise Psychology Laboratory at the University of Wisconsin-Madison. RET group members will have blood samples drawn 1 hour before and 30 minutes following their first training session of the week during weeks 2, 7, and 15. Four tubes will be collected prior to exercise (40 ml) and four tubes after exercise (40 ml) at each of the three time points. Total volume of blood drawn over the duration of the study for participants in the RET group will be 240 ml. WLC group members will not be asked to provide blood samples.

Resistance exercise training and wait-list control interventions

We have designed a standardized (66), yet individualized, resistance exercise training program that is sensitive to the potential for symptom exacerbation in GVs with CMP while incorporating progressive increases in resistance. The program is designed to ensure that a training effect (i.e. strength gains) occurs for all adherent and able Veterans, but is realistic considering the population being studied.

Participants assigned to the exercise condition will be asked to perform resistance training twice per week for 16 weeks. All resistance training bouts will be supervised by trained exercise specialists who possess the necessary education and experience to do so. The minimum requirement to demonstrate possession of the necessary education and experience for this position will be one of the following: certification with a nationally recognized sports medicine agency (for example ACE, ACSM, NSCA), completion of a graduate level course involving clinical exercise testing and prescription, or an advanced degree in exercise science. Exercise training will be conducted in a resistance training facility created specifically for this study at the Madison VA hospital (G2/G4). RET will be conducted on an individual basis to avoid potential mental health benefits accruing from social interaction with group exercise (67). This will help ensure that any detected benefits are specific to the exercise intervention. The exercise specialists will be available throughout the day, including weekends, to allow for flexible workout schedules and increase adherence to the program. If, because of an injury, illness or medical condition unrelated to their study participation, a participant is forced to take an extended layoff, more than 4 weeks, from exercise training, we will offer those individuals the option of restarting the 16-week exercise intervention. If the participant opt to restart the intervention we will also ask them to complete additional, but not more than 3, MRI scans to correspond to their new starting date.

Published methods will be employed to instruct participants on how to perform resistance exercise (68). Great care will be taken to educate participants on how to safely use the exercise equipment. Safety drills will be conducted with each participant at the outset of the training program, and the participants will be monitored during each session. Each participant will be required to practice correct breathing techniques (e.g., avoiding Valsalva). Maximal lifts will never be allowed. Very light loads (e.g. 30% of 4 repetition maximums) will be used

during the first week so participants learn proper breathing and lifting techniques, and habituate to the exercise.

After the initial habituation period, each resistance exercise bout will involve the completion of seven to ten exercises preceded by a warm-up. The exercise specialist will work with each Veteran to determine whether all ten exercises can be completed in a given session. Each moderate intensity exercise will be preceded by a single set of the exercise at a very low intensity for the purpose of providing a warm up for the specific muscles involved in the exercise. There will be a minimum of one minute of rest between each exercise and an additional two minutes rest between each set. Water will be available and the participants will be encouraged to drink plenty of water to stay hydrated.

Follow-up at 6 and 12 Months

Follow-up testing will consist of similar procedures to testing at weeks 6, 11 and 17. Participants will be asked to wear an accelerometer for the week preceding their test session. Subjects will return to the Waisman Center to complete a questionnaire battery intended to gauge their clinical symptoms and self-reported physical activity and to undergo psychophysical pain testing while their brain responses are monitored in the MRI scanner.

Pilot Scans

Pilot subjects will be asked to complete a scanning protocol which is identical to the procedures for participants of the full protocol with one exception; Pilot subjects will be asked to refrain from rating a proportion of the thermal stimuli to which they are exposed. The data collected from the pilot scans will be used to compare brain responses to thermal stimuli alone and in conjunction with the cognitive task and rating procedure. We expect the information we gather during the pilot sessions to improve our ability to accurately model the brain responses of study participants who complete the full protocol.

Safety Monitoring Plan

Clinical Interview and Clinical Assessment

Clinical interviews (psychiatric) and assessments (rheumatologic) will be conducted following written informed consent on the first day of testing. For purposes of confidentiality, all interviews will be conducted in a private office at the Madison VA Hospital. In addition, information regarding substance use and/or abuse will be used only to determine eligibility. The clinical assessment will also be conducted in a private room in the Madison VA.

In the rare event that a subject experiences significant distress during the interview (as determined by the clinical interviewer or expressed by the subject) they will be given Dr. Lickel's contact information (phone contact) and informed that they can contact him to discuss their situation, and to get additional and proper referral. In extreme distress situations (i.e. suicidal circumstances), the clinical interviewer will contact emergency services in the area where the subject is residing (home or the lab).

If an individual is excluded from participation based on the results of either the clinical interview or clinical assessment, the single original copies of the interview and assessment forms will be stored in a locked cabinet in the UW Exercise Psychology Laboratory under the supervision of the PI, Dr. Dane Cook. No data from the interview or assessment forms of excluded subjects will be entered into the electronic study database.

Psychophysical and Cognitive Testing

If a subject becomes significantly distressed during testing in either the MRI simulator or 3T MRI unit, they will be given Dr. Lickel's contact information and informed that they may contact him to discuss their situation.

Interviews and Questionnaires

Answering some of the items on the questionnaires and participating in the clinical interview may make subjects uncomfortable. For the clinical interview, administration of the MINI will only be conducted by trained study personnel. Study personnel will be instructed to handle distress situations according to the emergency procedures set forth by the VA. Risk is minimized by scheduling subjects in a timely fashion as well as providing subjects with 24-hour contact information for immediate referral and withdrawal from study. Although

we will recruit subjects who may have a diagnosis of depression, suicidal ideation is not expected to occur. In the rare event that a subject becomes suicidal while they are in the study, that subject would be dropped from the study and referred for immediate treatment (Supervised by Dr. Lickel).

Blood Draws

There may be a risk of slight discomfort for participants when the blood is drawn from the arm. The main risks associated with having blood drawn may include infection, bruising, redness, discomfort, or bleeding at the needle puncture site. Participants will be warned of these risks and encouraged to contact the PI and their personal physician should they experience any ill effects of having blood taken. If participants elect not to have blood drawn, their decision will in no way impact their eligibility for the present study.

We will be conducting a genetic analysis of all collected blood samples. Related to this, participants will be made of aware of risks associated with the accidental release of genetic information, such as negatively affecting their ability to obtain health insurance or workplace discrimination. If participants elect not to provide a tissue sample for storage, their decision will in no way impact their eligibility for the present study.

Confidentiality

Risks to confidentiality will be minimized by keeping the lone copy of the document linking study assignment number and the participant's unique identifiers with the participant's informed consent in a locked cabinet in the Madison VA laboratory of Dr. Cook (G2). Only subject numbers will be used for group assignment, data processing and analyses. fMRI data will be stored in a password protected area with firewall protection at the Waisman Laboratory for Brain Imaging and Behavior and electronic behavioral data will be stored in an encrypted file on a firewall- and password-protected server in the UW Department of Kinesiology. The risk of the accidental disclosure of results from the genetic analysis will be minimized by not labeling the sample with any personal identifiers and using only the subject's unique study number. In addition, we will not purposely disclose any results to subjects or their representatives. Only authorized study personnel will have access to personally identifiable information and the sole document which links that information with the coded results. Collected blood samples will be used up in the process of analysis and no specimen samples will be stored for future research. As a further precaution and in an effort maintain subject privacy, we have applied for a Certificate of Confidentiality.

In addition to ensuring that all members of our study team remain current on all required training related to privacy and confidentiality (i.e., Human Subjects, Privacy, Information Security and HIPAA), removal of access to research study data will be accomplished when they are no longer part of the research team. In the event of an actual or suspected data breach (e.g., theft or loss of data, unauthorized access to sensitive data) we will, in accordance with VA policy, notify the VA Information Security and Privacy Officers, the VA Associate Chief of Staff for Research, and the UW IRB within an hour of the discovery of the incident.

MRI Safety

-The following are risks associated with the fMRI procedure. They will be controlled by screening subjects for potential risk factors and by following standard imaging safety protocols:

Implants/Prostheses

The magnetic field of the MR system exerts a force on ferromagnetic objects within the field. This force can cause a ferromagnetic implant, such as an aneurysm clip, surgical clip, or prosthesis, to move or be displaced and cause injury or death. If the implant is large, sufficient currents can be induced in the metal by the magnetic field (eddy currents are induced by pulsed gradient fields) to cause heating of the implant. **Any subject with any type of implant will be excluded from the study.**

Pregnancy and infants

The safety of the radiation involved in the MR system when used to image fetuses and infants has not been established. **Therefore, women who are pregnant or suspect they might be pregnant are excluded.**

Collision Hazard

The magnetic field near the MR system is strong enough to attract ferromagnetic objects with great force. Near the magnet this force can be strong enough to pull objects in and cause them to fly down the axis of the magnet. Such objects become projectiles that can cause injury or death. The user must establish a security zone to prevent ferromagnetic objects from coming into proximity of the magnet. ***Such a security zone has been established with great care in our lab.***

RF and Magnetic Field Interference

Electronic implants, such as cardiac pacemakers, may be susceptible to interference from the magnetic and RF fields produced by the MR system. This interference may destroy or negatively affect operation of these devices. Since interference to cardiac pacemakers is observed in magnetic fields as low as 13 gauss, ***means have been provided to prevent persons with cardiac pacemakers or other implanted electronic devices from entering a zone where the magnetic field exceeds 5 gauss.***

Quench Hazard/Asphyxiation Risk

In normal operation, the cryogenics in the magnet of the MR system are vented into the ducting in the magnet room that carries the gases to the outside. If the magnet quenches, the boil-off rate will increase. If the ventilation system is not adequate or fails, the vented gases can fill the room with extremely cold, dense gaseous helium and nitrogen and cause asphyxiation. ***At both the Waisman Center and the UW Hospital, gases are vented directly to the outside in accordance with the instructions given in the installation directions.***

RF Antenna Effects

If metal wires or electrodes, such as electrocardiograph (ECG) leads, are attached to the subject during imaging, the RF energy radiated by the imaging coils of the MR system can induce sufficient electrical currents in the lead wires to cause burns where the electrodes or wires contact the skin. ***The scanner operator(s) will inspect any such leads and arrange them so that the risk of induced currents is minimized.***

Biomagnetic Hazards

It is possible that subtle genetic or molecular changes could be caused by the magnetic fields produced by the MR system. To date, however, no harmful biological effects have been demonstrated at the magnetic field strengths and exposure times utilized by the MR system. At the present time, the likelihood of any significant biomagnetic effect is considered to be very low.

Neurostimulation

Some subjects undergoing echo-planar imaging have experienced minor neurostimulation effects, such as muscle twitches and “tingling” sensations, due to the rapidly oscillating magnetic field gradients used in these examinations. There are no known risks associated with these effects. Specifically, the potential for cardiac stimulation has been examined and judged not to be a problem (see Protocol #94-832-193 for documentation). ***The devices used in our research do create field gradients that are within the limits specified by the FDA. The head resonator for the Waisman and UW Hospital scanners operates within FDA guidelines.***

Clinical Hazards

The confining conditions of the MR system can precipitate claustrophobia in a subject. ***Subjects are screened for possible claustrophobia before they are enrolled in the study.***

Access to MR Area

Access to all areas exceeding the 5 gauss level will be controlled by warning signs, barriers, staffed entry locations, or adequate interrogation to assure avoidance of incidents. ***Access to the magnet room by any personnel will be closely controlled for safety of persons, in particular to prevent accidental introduction of ferromagnetic objects that could be attracted by the magnetic field generated by the***

MR system. All study staff that will enter the MR Area in the course of their duties are required to complete a MRI safety screening and view a safety video on working in the MR environment.

Procedures for pregnancy screening

We will ensure that women who are pregnant or who are unsure of their pregnancy status do not participate in the study. Pregnancy status is obtained at three levels of our experimental procedures. First, we ask at the phone screen if the subject is or is trying to become pregnant. If they answer yes to either of these inquiries they are excluded from participating.

Second, we ask that they read and understand the statement at the end of the consent documents that states:

PREGNANCY STATUS – FEMALE SUBJECTS ONLY

The regulations for this type of research do not allow the participation of female subjects who are pregnant. Female subjects are therefore asked either to sign the following statement, or to have a pregnancy test performed before proceeding. Please sign this statement only if you are certain you are not pregnant. If you are not certain, please do not sign this statement, but ask the Investigator to perform a pregnancy test before proceeding.

I confirm that I am not pregnant.

Signature of Subject

Date

If they do not sign this statement acknowledging that they know they are not pregnant, they cannot participate. Finally, our MRI technicians ask all female subjects to confirm that they are not pregnant prior to entering the scanner.

Procedures for Adventitious Findings for MRI

We have opted to disclose **no** incidental or adventitious findings to subjects, whether clinically significant or not. As such the images we collect as part of our MRI scans will **not** be read by a qualified reviewer. Participants will be informed in the consent document that the images will **not** be read by neuroradiologist and **no** incidental or adventitious findings will be reported to them. If, by some circumstance, the P.I. becomes aware of a condition which is of such clear clinical significance (e.g. brain tumor) that he feels compelled to tell the subject, the P.I. will contact the IRB immediately for guidance in determining how to proceed in potential reporting.

Statistical Considerations

Power estimates for the trial are based on Specific Aim 1. General multivariate regression models will be used to estimate the time averaged difference in pain ratings and clinical symptom scores (continuous measurements) between the treatment and the control group. With general multivariate regression models we model both the dependence of the response on the explanatory variables as well as the autocorrelation among the responses. In order to achieve 90% power, at alpha equal to .05, with an effect size of .6 (minimum effect size of clinical importance) and with a correlation of .6 between measurements from each individual, the necessary sample size would be 34 subjects per group. If we take into account a 20% subject attrition rate, then the total sample size should be 41 subjects per group. All randomized subjects will be included in the analysis within the appropriate arm that they were randomly assigned (i.e. an intent-to-treat analysis will be used). Noncompliance, protocol deviations, withdrawal or any other problem that occur after randomization will be ignored and the participant's last observed data points will be carried forward in the analyses. Missing data will be assumed to be missing completely at random and appropriate missing data methods will be used (i.e. multiple imputation) to minimize the effect of withdrawal. For the purpose of evaluating Specific Aim 2, a similar methodology will be employed to estimate the time averaged difference in physical activity counts as measured by accelerometry.

To estimate the impact of RET on BOLD responses to pain stimuli we will use a two-sample Hotelling's T-square approach. This will test differences in the vector of means of BOLD response from pain stimuli for the control and exercise group between the baseline (before treatment) and end of the study (after treatment) for three different brain regions (anterior cingulate, insula and middle frontal cortices). These regions were chosen based on the robust brain responses observed in patients with CMP. Hotelling's T-square is a generalization of the Student's t statistic that is used in multivariate hypothesis testing. If there are q variables, the null hypothesis is that the means of variables in the first population equal the means of variables in the second population. For each subject in each group the difference between baseline value and end of the trial value for all brain regions will be computed and a Hotelling's T-square will be performed to compare the mean difference vectors for each group. With a sample size of 34 subjects we will have 80% power to detect a moderate effect size ($\sim .6$), in the treatment group, between baseline and the end of the trial.

Secondary analyses may also be conducted on particular brain regions or a set of brain regions (known as a mask) as defined by the Harvard Oxford Atlas. Estimates of voxel-based power, determined by detecting moderate signal changes (0.5% to 1.5%) and basing power on a noncentral t-distribution method, indicate that for most brain regions of interest a sample size of 12 subjects per group in the 'pain' condition provides power of 0.8 for rejecting the null hypothesis at an uncorrected α of .005 assuming robust pain-related activity (signal change $\sigma_B=0.3\%$), a moderate difference level for groups and greater than 100 time points in the 'pain' condition (69). Our preliminary data from our NIH project indicate robust responses to our experimental manipulations with sample sizes as small as 5 ($n=5$ RA group, $n=11$ Con, $n=14$ FM). For group comparisons, our preliminary NIH data indicate large effects between groups for FM patients compared to controls in several hypothesized regions. Significant differences ($p<0.01$) between patients and controls for the 'pain' condition occurred in several regions including the IC ($t=3.6$) and frontal cortex (BA 10; $t=3.7$). For the pain plus distraction condition we found significant differences ($p<0.01$) in several regions including the orbitofrontal (Con > FM, $t=3.3$) and IC (FM > Con, $t=3.5$). Effect sizes (d) for these differences ranged from 1.36 to 1.53. Assuming an α of 0.01 and a conservatively large effect size of $d=0.80$, 11 subjects per group would provide power of 0.9 to detect differences in the Main Effect for either pain or pain plus distraction conditions. Therefore our sample sizes of 12 per group should provide sufficient power to detect significant differences when they are present.

To study the joint effect of the BOLD response values as well as FA and MD values from DTI measurements, random coefficient mixed models will be used. Random coefficient mixed models assume that the regression coefficients are a random sample from a population of possible coefficients and allows modeling the variation between the study units (70). As in the case with multiple response variables (multiple brain regions), a separate set of regression coefficients will be fitted for each response variable and the correlation among these random coefficients can be examined.

Data and Record Keeping

The P.I. will oversee the data collection, entry, and management in association with study staff assigned to those duties. Everyone involved in the collection of data will be trained to ensure data quality and proper conduct with the participants.

Data Management

Study data will be managed by the study coordinator (Stephanie Van Riper) under the supervision of the P.I. and study scientist (Dr. Aaron J. Stegner). All data collected with and stored on the laptop will be coded and encrypted. No personally identifying information will be entered into the laptop database. The laptop is encrypted with technology that is FIPS 140-2 validated (Madison VA IRM installation) in addition to being password- and firewall protected. Only study personnel involved in data collection will have physical access to the laptop. All coded study data collected on the study laptop will be downloaded on a biweekly basis to the electronic study database maintained in an encrypted file on a password- and firewall-protected server.

Procedures to Maintain Confidentiality

If an individual is excluded from participation based on the results of either the clinical interview or clinical assessment, the single original copies of the interview and assessment forms will be stored in a locked cabinet in UW Exercise Psychology Lab under the supervision of the PI, Dr. Dane Cook. No data from the interview or assessment forms of excluded subjects will be entered into the electronic study database. Participants who are enrolled will be given an individual identification number (ID#) which will be used to collect data. This will also maintain the participants' confidentiality. For the purpose of data analysis, all subjects will be referred to using only their ID#. Staff members involved in the data management and analysis that do not have direct contact with participants should and will be blind to the identity of participants' data. The key that links the participant to the ID# will be accessible only to people deemed necessary by the investigators.

Maintaining Study Records

Per VA guidelines all study records and data will be maintained for 6 years following the completion of study-related activities. Following that 6-year period, all VA-owned information will be securely returned to the VA and only non-VA owned data can and will be destroyed. Maintaining these study records poses no significant risk to privacy or confidentiality because the investigators will manage access to these records. The electronic databases will be permission and/or password protected. Any paper copies will be kept under lock and key and managed by the lead investigator.

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