PI: **COOK, DANE B**	Title: Impact of exercise training on pain and brain function in Gulf War Veterans	
Received: 12/08/2009	FOA: CX09-013	Council: 05/2010
Competition ID:	FOA Title: CSR&D AWARD FOR RESEARCH ON NEW TREATMENTS FOR GULF WAR VETERANS' ILLNESSES	
1 I01 CX000383-01	Dual:	Accession Number: 3253570
IPF: 481071	Organization: WM S. MIDDLETON MEMORIAL VETERANS HOSP	
Former Number:	Department:	
IRG/SRG: SPLD	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 221,700 Year 2: 207,000 Year 3: 245,700 Year 4: 285,900 Year 5: 287,500	Animals: N Humans: Y Clinical Trial: N Current HS Code: 20 HESC:	New Investigator: N Early Stage Investigator: N

Senior/Key Personnel:	*Organization:*	*Role Category:*
Dane Cook	WM S. MIDDLETON MEMORIAL VETERANS HOSP	PD/PI
Andrew Alexander PhD	University of Wisconsin School of Medicine and Public Health	Other (Specify)-Co-Investigator
Lisa Colbert PhD	University of Wisconsin School of Medicine and Public Health	Other (Specify)-Co-Investigator
Dana Tudorascu PhD	University of Wisconsin-Madison	Other (Specify)-Co-Investigator
Patrick O'Connor PhD	University of Georgia	Consultant
Dean Krahn MD	William S. Middleton Memorial Veterans Hospital	Other (Specify)-Co-Investigator
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Summary

The overall aim is to determine the efficacy of resistance exercise training (RET) for the treatment of Gulf War Veterans (GVs) suffering from chronic musculoskeletal pain (CMP). In addition, we will assess the influence of RET on total physical activity levels, pain sensitivity and pain regulation, and brain white matter tracts. By applying functional neuroimaging techniques in conjunction with pain psychophysics, we will be able to determine how the brains of Veterans with CMP respond to pain and whether these responses can be modified by RET. We plan to use blood oxygen level dependent (BOLD) and diffusion tensor imaging (DTI) methods in conjunction to evaluate 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 physical activity behaviors. The primary goals of this project will be accomplished by comparing GVs with CMP assigned to RET with those assigned to wait-list control (WLC) in a randomized controlled trial. The specific aims of the project are to determine the influence of RET on: 1) pain symptoms, physical function, and patient global impression of change (PGIC); 2) total daily physical activity levels; 3) brain mechanisms of pain ***sensitivity*** and ***regulation***; and 4) pain-relevant brain white matter tracts involved in pain processing and control. Sixty-four Veterans will be randomly assigned to either 16 weeks of either RET or WLC. Follow-up assessments of primary and secondary outcomes will occur at 6 and 12 months post RET and WLC. RET will consist of exercises that target the entire body and gradually progress from low to moderate intensity loads over time. Total work will be measured during exercise to demonstrate a training effect. Physical activity levels in both groups will be assessed via self-report and accelerometry methods. Physical activity will be assessed at baseline; at weeks 5, 10, and 16 of RET and WLC; and at 6- and 12-month follow-ups. Pain sensitivity and pain regulation will be assessed using pain psychophysical and functional magnetic resonance imaging methods. Pain sensitivity and pain regulation will be assessed at baseline; at weeks 6, 11, and 17 of RET and WLC; and at 6- and 12-month follow-ups. Brain white matter tract structure will be determined using DTI methods and will be assessed at baseline; at weeks 6, 11, and 17 of RET and WLC; and at 6- and 12-month follow-ups. We expect that by the end of the trial, GVs with CMP assigned to RET will show: 1) statistically significant and clinically meaningful improvements in self-reported pain, physical function & PGIC and secondary outcomes (sleep, self-esteem, fatigue, anxiety and depression); 2) increases in total physical activity that are attributable to an increase in RET; 3) decreased pain **ratings** and decreased **brain** responses to experimental pain stimuli; 4) ***decreased*** brain responses in areas that process the sensory aspects of pain and ***increased*** brain responses in areas that modulate or inhibit pain processing during a distracting cognitive task; and 5) improvements in DTI measures of brain white matter tract structures. The goals of this project are consistent with the Department of Veterans Affairs' call for "Research on New Treatments for Gulf War Veterans' Illness" by proposing a controlled clinical trial 1) in a clearly defined Gulf War Veteran population with a specific symptom (CMP), 2) with appropriately defined and clinically meaningful endpoints, and 3) that identifies potential biomarkers that are explanatory or predictive of a treatment response. No efficacious treatments have been identified for GVs with CMP; however, resistance exercise training remains an inadequately explored yet promising treatment based on successful trials with civilians suffering from chronic pain. We have designed a resistance exercise treatment trial that has the potential to benefit Veterans' health and to begin to determine potential mechanisms of pain maintenance in CMP.

PI: **KEARNEY, DAVID J**	Title: A randomized controlled trial of a mindfulness based intervention for Gulf War Sy	
Received: 12/10/2009	FOA: CX09-013	Council: 05/2010
Competition ID:	FOA Title: CSR&D AWARD FOR RESEARCH ON NEW TREATMENTS FOR GULF WAR VETERANS' ILLNESSES	
1 I01 CX000313-01A1	Dual:	Accession Number: 3255181
IPF: 481094	Organization: VA PUGET SOUND HEALTHCARE SYSTEM	
Former Number:	Department: Research	
IRG/SRG: SPLD	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 96,605 Year 2: 99,995	Animals: N Humans: Y Clinical Trial: N Current HS Code: 20 HESC:	New Investigator: N Early Stage Investigator: N
Senior/Key Personnel:	*Organization:*	*Role Category:*
David Kearney MD	VA Puget Sound Health Care System	PD/PI
Stephen Hunt MD,MP	VA Puget Sound Health Care System	MPI
Charles Maynard PhD	University of Washington & VA HSR&D	Other (Specify)-Investigator
Kelly McDermott PhD	VA Puget Sound Health Care System	Other (Specify)-Statistician
Kathleen Pagulayan PhD	University of Washington & VA Puget Sound Health Care System	Other (Specify)-Investigator
Tracy Simpson PhD	University of Washington & VA Puget Sound Health Care System	Other (Specify)-Investigator

Additions for Review

Updated Pages	Checklist - Kearney		12/17/2009
Updated Pages	Other Support - Kearney	Other Support documentation for all Key Personnel	12/17/2009

Abstract

Background: Many military personnel who participated in the Gulf War in 1990-1991 reported negative health consequences subsequent to the deployment. The most prevalent of these health concerns involves a triad of unexplained physical symptoms (fatigue, arthralgias / myalgias and concentration/memory disturbances) commonly referred to as "Gulf War Syndrome," which for many continues into the present. No clear, unifying pathophysiological process or etiologic agent has been identified for Gulf War Syndrome (GWS). Training in mindfulness has been shown to result in reduced stress perception and improved quality of life for individuals with symptoms akin to those associated with GWS. Mindfulness involves bringing attention to present moment experience, including cognitions and bodily sensations without judgment. The most common format for teaching mindfulness in the health care setting is through an 8-week class called Mindfulness-Based Stress Reduction (MBSR).
Aims: **1.** To assess the safety and feasibility of recruiting and retaining veterans with GWS to complete a study that involves randomization to treatment as usual (TAU) or TAU plus MBSR. **2.** Obtain symptom-based outcome measures for veterans with GWS, before and after randomization, to assess fatigue, pain, cognitive function, physical functional status. **3:** Obtain objective measures of attention, concentration, and working memory in order to assess if MBSR results in a change in these parameters.
Design: Two-arm randomized controlled trial (RCT) comparing MBSR and TAU. **Participants**: 60 veterans with GWS. **Intervention**: 8-week group-based MBSR based on Kabat-Zinn's model. **Assessment**: Three in-person assessments (baseline, post-treatment, 6-month follow-up) will include symptom measures of pain, fatigue and cognitive failures, as well as objective measures of attention and memory (PASAT, Trail making test A/B, California verbal learning test, symbol digit coding and digit span test). **Hypotheses and Analyses:** We hypothesize that the intervention and study protocol will be acceptable to patients and we will be able to recruit at least 60 GWS veterans willing to participate. We also hypothesize that at least 80% of those randomized to MBSR will complete 4 or more treatment sessions and at least 85% of study participants will be assessed at each follow-up point. We anticipate that MBSR will have improved patient-reported outcomes, and improved measures of concentration and working memory, as compared to TAU. We will compare MBSR versus TAU at baseline and follow-up to determine whether MBSR is associated with changes in pain, fatigue, cognitive failures, physical component summary score of the SF-36-V, attention, concentration and working memory. If improvement in outcomes is associated with MBSR, this would support performing a larger clinical trial of MBSR for GWS.

PI: **SHETTY, ASHOK K.**	Title: Memory and Mood Enhancing Therapies for Gulf War Illness	
Received: 12/03/2009	FOA: BX09-014	Council: 05/2010
Competition ID:	FOA Title: BLR&D AWARD FOR RESEARCH ON GULF WAR VETERANS' ILLNESSES	
1 I01 BX000883-01	Dual:	Accession Number: 3249872
IPF: 481065	Organization: DURHAM VA MEDICAL CENTER	
Former Number:	Department: Research & Development Service	
IRG/SRG: SPLD	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 339,286 Year 2: 328,572 Year 3: 328,572 Year 4: 328,572	Animals: Y Humans: N Clinical Trial: N Current HS Code: 10 HESC:	New Investigator: N Early Stage Investigator: N
Senior/Key Personnel:	*Organization:*	*Role Category:*
Ashok Shetty	Durham VA Medical Center	PD/PI
Bharathi Hattiangady	Duke University Medical Center, Durham VAMC (WOC)	Other Professional-Research Scientist
Vipan Parihar	Duke University Medical Center, Durham VAMC (WOC)	Post Doctoral Associate

Principal Investigator/Program Director (Last, first, middle): Shetty, Ashok, K.

PROJECT SUMMARY STATEMENT

While the Gulf war illness displays multiple central nervous system (CNS) impairments, cognitive dysfunction, memory loss, depression and anxiety are the most common symptoms. Intake of the prophylactic drug pyridostigmine bromide (PB), prolonged exposure to pesticides (such as DEET and permethrin), and the combat-related stress during the Persian Gulf War-1 are believed to be the underlying causes of Gulf war illness. Consistent with this supposition, studies in our laboratory using a rat model demonstrate that a combined exposure to low doses of the above chemicals (PB, DEET & Permethrin) and mild stress for 28 days causes considerable impairments in the hippocampus-dependent functions, which include impaired ability for new spatial learning, declined ability for making new memories, and increased depressive- and anxiety- like behavior. Analyses of hippocampal tissues further revealed that the behavioral impairments are linked with greatly declined neurogenesis but mostly intact neuronal cell layers in the hippocampus. Considering the role of hippocampal neurogenesis in learning, memory and mood functions, these findings suggest that a greatly declined neurogenesis likely underlies learning & memory impairments and increased depression & anxiety in Gulf war illness. In this context, strategies that greatly enhance hippocampal neurogenesis appear useful for reversing the cognitive dysfunction and the depression and anxiety observed in Gulf war illness. Indeed, our preliminary studies suggest that administration of antidepressants such as fluoxetine (FLU) or rolipram (ROL) after a combined exposure to chemicals (PB+DEET+Permethrin) and stress has promise for improving the hippocampal neurogenesis as well as cognitive function. **Therefore, using the above rat model of Gulf war illness, we propose to rigorously analyze the efficacy of distinct clinically applicable strategies for enhancing the hippocampal neurogenesis & cognitive function, and reversing the depressive & anxiety-like behaviors.** In Specific Aim 1, we will test the hypothesis that combined applications of an anti-depressant drug (FLU or ROL) and an antioxidant drug (Curcumin [CUR] or Resveratrol [RESV]; dietary supplements having anti-oxidant, anti-inflammatory, and neurogenesis enhancing properties) greatly enhance hippocampal neurogenesis, cognitive function and mood in the rat model of Gulf war illness. In Specific Aim 2, we will address the hypothesis that combined applications of an anti-depressant drug (FLU or ROL) or an antioxidant drug (CUR or RESV) and physical therapy such as the voluntary physical exercise (PE) greatly boost hippocampal neurogenesis, cognitive function as well as mood in the rat model of Gulf war illness. In both aims, we will first expose rats to the three chemicals (PB, DEET & Permethrin) and mild stress (i.e. 5 minutes of restraint stress) for 28 days and ascertain the extent of cognitive dysfunction and depressive & anxiety-like behaviors. Animals will then receive the treatments as described above and undergo testing at 6-weeks after the conclusion of the treatment for cognitive function and depressive & anxiety-like behavior. Following this, their performance in the behavioral tests will be correlated with the extent of hippocampal neurogenesis, the proliferative behavior of neural stem cells (NSCs), and the pattern of expression of genes related to neurogenesis and to suppression of oxidative stress. The overall research is designed to ascertain the therapeutic efficacy of different treatment approaches. **Thus, the studies proposed in this project are highly relevant to the Gulf war RFA (BX-09-014) because, this project utilizes a rat model that simulates the various exposures experienced by the Persian Gulf War-1 veterans and the experiments are focused on developing therapeutic strategies for reversing several CNS impairments associated with Gulf war illness.**