PI: **COOK, DANE B**	Title: Impact of exercise training on pain and brain function in Gulf War Veterans	
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Competition ID:	FOA Title: CSR&D AWARD FOR RESEARCH ON NEW TREATMENTS FOR GULF WAR VETERANS' ILLNESSES	
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IPF: 481071	Organization: WM S. MIDDLETON MEMORIAL VETERANS HOSP	
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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

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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.