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13. SUPPLEMENTARY NOTES

14. ABSTRACT- A better understanding of the nature of chronic pain after combat related to TBI is of central importance in the treatment of warfighters who suffer from this condition. The broad objective of this work is to characterize the neural networks involved in post-traumatic pain using functional MRI both in the resting state and during activation with a moderately painful stimulus. The hypothesis is that the patterns of activation under both conditions are abnormal and similar to those in other chronic pain states such as migraine and fibroyalgia when controlled for co-morbid insomnia, depression and PTSD. The study groups to be compared for this work include patients with chronic migraine, fibromyalgia, post-traumatic pain post mTBI, asymptomatic individuals post mTBI, and normal controls. Resting state network characteristics will be determined by MRI at rest and contrasted to the pattern of activation during a visual attention task. Next, a calibrated degree of moderate pressure will be applied to the left thumb. Resting state fMRI data will be compared between groups and a general linear model including the scores on the depression, insomnia and PTSD inventories will be tested. The impact of this research will be a better characterization of the disturbances within the central nervous system that cause and propagate pain after mild TBI to lead to improved strategies to treat this.

15. SUBJECT TERMS- mild TBI, functional MRI, resting state, neural works

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INTRODUCTION: This is a prospective study designed to characterize pain pathway activation in the brains of mild traumatic brain injury patients with chronic pain, and to compare with other demographically-matched individuals with and without chronic pain disorders. The specific study groups to be compared for this work include patients with chronic migraine, fibromyalgia, post-traumatic pain post mTBI, asymptomatic individuals post mTBI, and normal controls The understanding of the neurobiology of chronic pain and mTBI uses magnetic resonance imaging (MRI) methods to quantify the structural changes and functional activation patterns at rest and during *task* performance associated with chronic pain in TBI. A major emphasis of our study is to understand the connectivity of regions associated with chronic pain.

Structural imaging metrics involve high resolution MRI for grey matter analyses and DTI to assess white matter connectivity. Resting state fMRI is used to develop a neural network model of functional connectivity within regions of interest (those known to be part of the classic pain matrix and the so called "default" mode, a network that regulated higher cortical processing). The broad objective of this work is to gain a better understanding of the pattern of resting state connectivity in chronic pain and use these data to differentiate chronic pain in TBI from normal and other pain states. We will also use task fMRI to assess the regions activated during pain stimulation in each subject group and to then conduct effective connectivity analysis that will allow us to probe which connections are modulating others in the pain pathway of individuals who suffer from chronic headache and somatic pain after mTBI using non-invasive brain imaging methods. Imaging data will be correlated with behavioral data and be used to understand the neural networks involved in chronic pain in the experimental group when controlling for comorbid PTSD, life stress, depression and insomnia. The intent is to more fully characterize the nature of pain pathway abnormalities and use this information to develop measures that assist in differential diagnosis of pain syndromes, provide a metric of treatment responsiveness, and be used to predict treatment outcomes.

BODY:
The approved statement of work outlined the tasks to be completed:

Task 1 (months 1-6): Characterize resting state and mild pain stimulated neural networks in previously identified individuals with chronic pain. Two subtasks were identified, that included:

1) Enrollment of 150 participants from five experimental groups: chronic pain following mild traumatic brain injury (mTBI), those with fibromyalgia, chronic migraine without aura, asymptomatic individuals after mTBI, and in normal controls, and
2) MRI scanning and completion of the behavioral measures on all enrolled participants

Task 2 (months 18-21): Data analysis to include DTI, resting state network and fMRI analysis, and functional/structural imaging correlation.

Task 3 (months 21-24): Generate final report and publish results.

To complete subtasks two and three, following approvals and MRI sequence refinement, a phased recruitment strategy was implemented in September 2011. To date, five control

participants, five fibromyalgia patients, one migraine with aura, and one mild TBI patient have completed the study. One control patient scan is incomplete, and another control patient withdrew from the study after consenting. Two additional patients, one migraine without aura, and one control patient, are awaiting scanning.

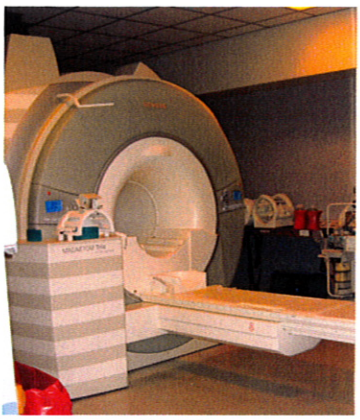

Figure 2. MRI scanner used for this study

Preliminary fMRI results from the first 10 patients show consistent activations in response to the moderately painful stimulus in all of the regions of the pain network (i.e. primary and secondary somatosensory regions, insula, cingulate, primary motor regions, thalamus and cerebellum). In the same subjects, fMRI during mental tasking has also shown consistent activation. Analysis of the DTI and resting state data for these subjects will be completed next, for quality assurance purposes.

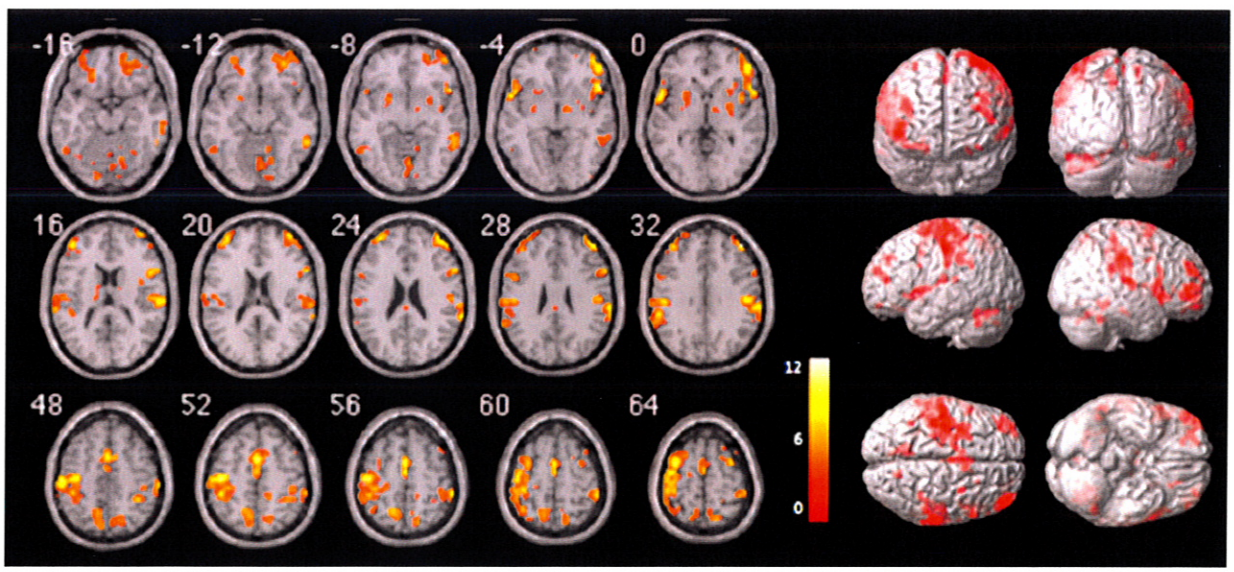

Figure 3. BOLD response for a single subject (migraine with aura patient). Activations shown are a result of the pain condition versus rest contrast and identify regions of the pain network. Transverse slices are shown on the left and a 3D rendered image is shown on the right.

Recruitment continues to be the major obstacle in the study for various reasons. First, the overall population of mTBI patients available to be enrolled in the clinic remains low; most are still being recruited primarily into the SCORE! (Study of Cognitive Rehabilitation Effectiveness for mild traumatic brain injury) and its associated MRI intensive counterpart iSCORE study. Fortunately recruitment for these studies will be completed soon, and recruitment efforts will be renewed with the TBI Service at SAMMC (San Antonio Military Medical Center, formerly BAMC-Brooke Army Medical Center) and the DVBIC Service (Defense Veterans Brain Injury Consortium) also at SAMMC. Second, though additional subjects have been included by expanding the AIs on this study and through increased awareness/publicity, the logistics of scanning subjects at a separate nonmilitary institution is daunting to some subjects. Third, the research coordinator hired at the time of the last report was quickly let go and the study lacks a suitable research coordinator able to spearhead recruitment as well as facilitate operations between SAMMC and the Research Imaging Center at UTHSCSA (University of Texas Health Science Center at San Antonio). The study has been extended for another 6 months and recruitment goals are now incorporated into the study.

Task 2 and 3. These will be completed upon enrollment of additional participants

KEY RESEARCH ACCOMPLISHMENTS:

- Successful development of an experimental paradigm to support this study, and future studies of chronic pain in active duty service members, veterans, and civilians.
- Analysis strategy for fully developed and we are getting excellent brain data (e.g., Figure above fMRI results).

REPORTABLE OUTCOMES:

Publications:

Lewis, JD, Wassermann EM, Chao W, Ramage AE, Robin DA, Clauw DJ, *Central Sensitization as a Component of Post-Deployment Syndrome*. NeuroRehabilitation 31(2012)": 367-372.

Presentations:

Robin DA, Lewis JD "Understanding the Mechanisms of Action of Chronic Pain in Warfighters with Mild Traumatic Brain Injury: Non-invasive Imaging Approaches", Presented at 3rd Federal Interagency TBI Meeting, June 2011.

Robin, DA, Parkinson, A, Manes J. Using quantitative meta-analytic techniques to understand the neural substrates of pain and chronic pain syndromes with VBM and fMRI data. Presented at University of Michigan Center for Chronic Pain and Fatigue. July 2011.

Robin, DA Using brain imaging to understand chronic pain and fatigue. Presented to Neuroscience Grand Rounds, UTHSCSA, September 2011.

CONCLUSION:

There continues to be an increased recognition of the problem of chronic pain following mTBI and deployment in active duty service members and veterans [2]. This study, despite its limitations, remains well-poised to contribute to an understanding of the changes in the brain that perpetuate pain in this population and other chronic pain conditions. In addition, it offers a platform for which to build clinical trials with an objective endpoint measure (fMRI activation to a painful stimulus), relevant to post-concussive symptoms.

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Central sensitization as a component of post-deployment syndrome

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Abstract. Many service members and veterans report chronic unexplained symptoms such as pain, fatigue and memory complaints, which have most recently been characterized as post-deployment syndrome (PDS). Chronic widespread pain is a component of this syndrome, producing significant disability and considerable health care costs. The similarity between the nature of these complaints and other medically unexplained illnesses such as fibromyalgia, irritable bowel syndrome, and chronic fatigue syndrome suggest that they may share a common mechanism. Here, we provide support for PDS as a consequence of pain and sensory amplification secondary to neuroplastic changes within the central nervous system, a phenomenon often termed central sensitization. We also discuss how factors such as stress and genetics may promote chronic widespread pain in veterans and service members who develop PDS.

Keywords: Chronic widespread pain, post-deployment, mild traumatic brain injury

1. Introduction

After military deployment, many service members and veterans experience unexplained symptoms, including pain, irritability, headaches, tinnitus, extremity numbness, fatigue, dizziness, and memory difficulty with long-term or permanent disability [11]. This syndrome was called "shell shock" during World War I and "postconcussional syndrome" during and after World War II, where it was attributed completely to combat and nearby explosions [38,39]. After the first Persian Gulf War [19,41,64], many veterans reported similar chronic symptoms, i.e., Gulf War Illness or chronic multisymptom illness. Citing personal accounts of illness after deployment, Cifu and Blake [11] used the term post-deployment syndrome (PDS) for the core set of symptoms in veterans of the current conflicts in Iraq and Afghanistan (OIF/OEF). While this aggregation of symptoms has traditionally been attributed to combat exposure, it is also true that in each war, troops who were not in the vicinity of fighting have developed the same syndrome [20]. Although the symptoms are varied, chronic widespread pain (CWP), involving the limbs, lower back and neck, has been increasingly recognized as a common symptom [11] that has no clear "cause" in more than 50% of reported cases [25].

The prevalence of post-deployment CWP in military veterans is high. In a survey-based, cross-sectional study of 12,000 United Kingdom (UK) veterans of the Persian Gulf War, Stimpson et al. [62] found that more than 16% of individuals deployed to the Gulf expressed symptoms of CWP. This prevalence equated to an adjusted odds ratio of 1.82 for those deployed versus those who served concurrently, but were not deployed. A high prevalence of CWP was also observed in a survey of

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more than 3,500 US veterans who served in the Persian Gulf War during the same time period [18].

Interestingly, the prevalence of CWP is conflict-specific. For instance, in the previously described UK study [62], those deployed to Bosnia instead of the Persian Gulf reported CWP no more often than non-deployed veterans, and those deployed to both regions had a prevalence equal to the Persian Gulf War group. A similar difference in unexplained symptoms, such as chronic fatigue syndrome, has also been noted between these cohorts [34,59], and has contributed to persistent speculation about an environmental exposure such as pesticide or depleted uranium as the cause of Gulf War Illness [13].

Large-scale studies of CWP in OIF/OEF veterans have not been completed, but preliminary data suggest the prevalence of CWP in veterans of OIF/OEF is similar, if not higher, than those of the Persian Gulf War. Within the VA system, 53% of those seeking medical care are classified as having "diseases of musculoskeletal system/connective system" that typically include chronic pain [66]. In a review of the records of 429 OIF/OEF veterans seen in a post-deployment clinic, 29% had pain in all four limbs [30].

The similarity between PDS and other medically unexplained conditions such as fibromyalgia [26,76], chronic fatigue syndrome [3,33,37], irritable bowel syndrome [74], post-concussion disorder [4,36], chronic headache [57], and post-traumatic stress disorder [43] has been previously noted [34]. In all these conditions, CWP occurs together with memory difficulties, fatigue, sleep disturbances and, often, depressed mood [75]. These syndromes are frequently seem in the same individuals; for example, the association between fibromyalgia and other conditions such as irritable bowel syndrome and migraine headaches was first reported nearly thirty years ago [74]. In an extensive review, Yunus [75] describes the common clinical features of several of these conditions and discusses how they share a hypersensitivity to cutaneous and visceral stimulation. In both animal models and humans, this hypersensitivity manifests as increased sensitivity to normally painful stimuli (hyperalgesia) and/or pain in response to normally non-painful stimuli (allodynia) [2, 69]. In addition, patients demonstrate hypersensitivity to non-somatosensory stimuli, such as lights, noises, and odors [23,24,32]. The terms "central sensitization" or "central augmentation" are increasingly used to describe these phenomena of increased pain and sensory transmission that produce the common set of symptoms in the previously listed disorders [2,68,69,71,72]. Specifically, individuals who have "centralized" their pain also complain of fatigue, insomnia, memory difficulties, and mood disturbances, perhaps because many of the same neurotransmitter systems that control pain and sensory sensitivity also control level of alertness, sleep, memory, and mood [69].

2. Central sensitization as a component of PDS symptoms

The term, central sensitization, was first used by Woolf (reviewed in [71]) to describe a spinal cord mechanism in animals and humans [45,50,51] secondary to peripheral nerve injury characterized by pain amplification, hyperalgesia, and allodynia. Recently, this term was used by Woolf and others to more broadly denote sensitization beyond the spinal cord to include the entire nervous system and particularly the brain. In functional neuroimaging studies, induced pain has demonstrated augmented neuronal activation in pain-processing regions in patients with CWP and other chronic pain states, particularly hyperactivity of the insular cortex [15,27] as compared to healthy controls. The uniqueness of this brain area to central sensitization is supported in animal models of chronic pain, where surgical lesions in the caudal granular insular cortex reduce allodynia without affecting normal mechanical stimulus thresholds [6].

The insular cortex is involved in many processes including sensory integration [16], working memory [61], and awareness of the physiological condition of the body. Neuroplastic changes in this region resulting from chronic pain (discussed in [46]) and other psychological or physiological stressors [60] are associated with several symptoms, e.g., memory difficulties, fatigue [65], sleep and mood disturbances [8].

Gulf War veterans have complained commonly of somatic and visceral hyperalgesia/allodynia [14,17], and the multitude of PDS symptoms closely match those previously associated with neuroplastic changes in the insular cortex that can occur with chronic pain. Together, these complaints suggest central sensitization as a potential mechanism for PDS.

3. Relationship between stress, military deployment and central sensitization

Stress appears to play an important role in developing chronic pain and its accompanying symptoms [49].

Table 1
Selected pharmacologic treatments for conditions in which central sensitization has been demonstrated

Condition	Pharmacologic treatments	References
Fibromyalgia	Duloxetine*, milnacipran*, pregabalin*, amitryptiline, paroxetine, citalopram	[8]
Irritable bowel syndrome	Imipramine, amitryptiline, gabapentin, pregabalin	[21,54]
Chronic fatigue syndrome	Amitryptiline, doxepin, citalopram, escitalopram	[53]
Chronic headache	Amitryptyline, nortriptyline, divalproex, propranolol, gabapentin, topirimate	[22]
Complex regional pain syndrome	Amytal, ketamine	[44]

*Food and Drug Administration approved.

This is supported in animal models, where fear learning and unpredictable sound stress produce increased pain sensitivity [28,56]. In humans, infections, accidental trauma, surgery, and other major life stressors can trigger regional or widespread chronic pain, fatigue, memory problems, and sleep disturbances [9,29,31,40, 42]. For instance, chronic threat of mortality from missile attack was associated with increased prevalence of CWP and somatic symptoms in Israeli civilians [1]. Coping style and cognition appear to mediate between chronic stress and pain development, with the possibility of pain-related fear, irrational belief that the situation is worse than it actually is, and avoidance amplifying peripheral sensations and increasing chronic pain [48, 60].

However, CWP is not a universal consequence of stressful life experiences. For instance, brief or indirect threat does not appear to be sufficient to produce CWP. As an example, after the terrorist attacks of 9/11, studies in Washington, DC and New York City regions showed no significant increase in pain or other somatic symptoms in individuals with fibromyalgia, or in the general population [47,55,68]. There is evidence for a genetic predisposition to CWP after a stressful life experience [58], and this likely extends to PDS in general.

It should not be surprising that some individuals deployed to war develop CWP accompanied by other somatic symptoms such as fatigue and memory problems, since this same phenomenon occurs after exposure to a broad variety of "stressors". For example, the 1958 British Birth Cohort Study led to many publications showing that individuals who early in life are involved in a motor traffic accident, the death of a parent, severe financial hardship, or a prolonged hospitalization, are 50–100% more likely to have CWP later in life than those that do not have these same exposures. Other known triggers of CWP include infections (e.g., Lyme disease, Q fever, Epstein-Barr virus), trauma (especially motor vehicle collisions), and "peripheral" musculoskeletal conditions such as arthritis that cause constant ongoing peripheral nociceptive input. Since individuals deployed to war may experience many of these triggers, the association between combat-related deployment and CWP is unsurprising.

4. The potential role of concussion in promoting central sensitization

While the somatic and behavioral complaints of Persian Gulf War and OIF/OEF veterans are similar, one important difference is the greater prevalence of concussion as a result of explosives, producing mild traumatic brain injury (mTBI) in OIF/OEF returnees. After concussion, approximately 5% or fewer of individuals have persistent complaints, including headache, tinnitus, fatigue, sleep disturbance and irritability [35]. In those patients with continued complaints, changes appear to occur in the brain over time. For instance, changes in gray matter volume, similar to those seen in fibromyalgia, have been previously noted in civilian patients with chronic posttraumatic headache [52]. Whether TBI itself causes these changes directly, or if they are a consequence of the accompanying chronic pain, stress, or other "non-kinetic" factors, is unclear and further research is needed to clarify this relationship.

5. Treatment approaches for conditions in which central sensitization is a component

Several treatments, both pharmacologic and non-pharmacologic, have been effective in treating conditions in which central sensitization has been demonstrated (see Table 1). Most medications for these conditions target pain processing in some fashion, and their use is supported by several randomized, controlled trials. Classes of compounds with the greatest efficacy across the various conditions include tricyclic antidepressants, dual action serotonin-norepinephrine inhibitors, and alpha 2 delta receptor ligands, such as pregabalin and gabapentin.

Intravenous amytal, a medium acting barbiturate, has been used to treat complex regional pain syndrome (CRPS) [44]. More recently, intravenous ketamine has shown promise in treating CRPS, as well [5]. Of the central sensitivity syndromes, this condition is unique in the use of these two medications.

In addition to medications, behavioral interventions have shown efficacy. For example, several randomized controlled trials of cognitive behavioral therapy strategies have have found clinically significant effects on pain and associated symptoms, such as, fatigue, and demonstrated increased function after treatment [67, 73]. The utility of these medical and behavioral interventions for treating PDS has yet to be determined.

6. Implications for rehabilitation and need for future research

Post-deployment CWP, as a component of PDS, has significant implications for public health. With 25% of 697,000 Persian Gulf War veterans reporting CWP [17] and almost 2 million troop-years deployed in support of OIF/OEF as of December 2008 [7], the health care -related costs of PDS are likely to be considerable: Average annual health care costs estimates for chronic pain treatment alone range from $13,000 to $19,000 per individual (1988–1997 dollars) [63]. CWP is associated with worse post-deployment health outcomes, independent of co-morbid health conditions, such as post-traumatic stress disorder and depression, and may represent the most debilitating feature of PDS [18,30].

Nearly 100 years after the "shell shock" epidemic of World War I, advances in understanding the neurobiology of chronic pain and cognition, coupled with sensitive structural and functional imaging techniques, finally offer the promise of dramatically improved awareness and rehabilitation of these symptoms associated with war. To date, the neurobiological basis for these symptoms has not been established, but there is sufficient overlap with conditions such as chronic fatigue syndrome and fibromyalgia to suggest central sensitization as a significant contributor. More research is clearly needed to confirm this association and would inform future treatment trials for CWP in veterans.

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