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Combat exposure is associated with cortical thickness in Veterans with a history of chronic pain

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ABSTRACT

Chronic Pain (CP) has been associated with changes in gray matter integrity in the cingulate and insular cortex. However, these changes have not been studied in Veterans, despite high prevalence rates of CP and interactions with combat-derived disorders. In the current study, 54 Veterans with a history of CP and 103 Veterans without CP were recruited from the Translational Research Center for Traumatic Brain Injury and Stress Disorders (TRACTS). Cortical thickness from structural MRI scans was determined using the FreeSurfer software package. Results showed that Veterans with CP showed a negative association between cortical thickness and levels of combat exposure in the left inferior frontal gyrus and superior parietal cortex, as well as the right rostral middle frontal gyrus, precentral and postcentral gyri and the superior temporal cortex. These findings suggest that CP may alter the relationship between cortical thickness and exposure to the stress of combat.

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1. Introduction

Chronic Pain (CP) is defined as pain that persists for longer than three months (International Association for the Study of Pain, http://www.iasp-pain.org/) and appears to be highly prevalent in Veterans of the recent conflicts in Iraq and Afghanistan. For example, one study has revealed that CP affected upwards of 50% of 685 Veterans seeking care in a Veterans Health Administration facility (Kerns et al., 2003), whereas other reports have indicated prevalence rates of 40% (Cifu et al., 2013). The presence of CP in Veterans is especially important since it is one of the main causes of disability (McWilliams et al., 2003; Patzkowski et al., 2012).

Chronic pain in Veterans appears to occur in a particular context of co-morbidities that may impact its diagnosis, treatment and outcome. Specifically, CP in Veterans occurs more frequently in individuals who are suffering from deployment-related disorders, such as Post-traumatic Stress Disorder (PTSD), and post-concussive symptoms related to mild Traumatic Brain Injury (mTBI) (Lew et al., 2013, 2009; Ullrich et al., 2013) than it does in individuals without these conditions. The co-occurrence of PTSD and CP was already shown to be as high as 80% in a sample of Vietnam era Veterans (Beckham et al., 1997), speaking to a possible link between psychological and physical pain. Investigators have hypothesized that CP and PTSD are not simply independent yet co-occurring factors, but that they might interact to create a cycle of mutual maintenance (Sharp and Harvey, 2001), which requires specific therapeutic approaches in treatment (Otis et al., 2009) to break. Further, the co-morbid presence of anxiety disorders and CP has been shown to be associated with greater use of opioid-based medication (Schwartz et al., 2006), resulting in an increased risk for abuse, dependence and overdose (Bohnert et al., 2014; Dobscha et al., 2013; Seal et al., 2012). Additionally, co-occurring CP and sleep disorders was present in 55% of a large sample of OEF/OIF/OND veterans and, together, accounted for 16% of cases in the sample who suffered from substantial disability (Lippa et al., 2015). There is furthermore a significant financial and human cost associated with treating comorbid CP and other deployment-related disorders (Beehler et al., 2013). For example, one study indicated a four-fold increase in costs of treating Veterans with co-morbid CP and psychiatric conditions (Taylor et al., 2012). There is therefore a critical need to better understand the contribution of

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CP to the psychological and physical burdens related to deployment experiences. However, such an investigation is constrained by the natural clustering of disorders observed in Veterans sample, which imposes the use of a multivariate approach to these complex conditions (Lippa et al., 2015).

In examining the effects of CP in Veterans, few studies have examined potential impacts of CP and its interaction with deployment-related conditions on the integrity of the brain. Nevertheless, advances in brain imaging methods have helped identify brain networks thought to support the sensation of pain, as well as areas susceptible to the effects of pain alone (Apkarian, 2011; Hayes and Northoff, 2012; Lumley et al., 2011). These networks have been operationalized across two dimensions representing the sensation of pain (somatosensory cortex) and the affective component of pain (cingulate cortex, prefrontal cortex and insula). Studies in civilian samples have shown that the diagnosis of CP itself was associated with decreased gray matter volume or thickness in the cingulate and insular areas (Apkarian et al., 2011; Baliki et al., 2011; Burgmer et al., 2009; Kuchinad et al., 2007; Rodriguez-Raecke et al., 2009; Schmidt-Wilcke et al., 2005; Valet et al., 2009), as well as in the dorso-lateral prefrontal cortex (Schmidt-Wilcke et al., 2006). Some studies (Apkarian et al., 2004; Valet et al., 2009) further found that the observed decrease in gray matter density in the clinical group was significantly associated with the duration of clinical pain, suggesting a model of gradual atrophy of gray matter due to the pain. Despite the elevated prevalence of CP and associated costs in Veterans, findings of decreased gray matter integrity have yet to be replicated in a sample of Veterans. Examining this specific population is important since the association between brain structures and CP in Veterans may differ from that observed in civilians due to the deployment-related comorbidities. If this is the case, such an exacerbation could significantly impact the integrity of the brain, the phenomenological experience of pain and the effectiveness of treatments designed for pain alone.

Examining the impact of CP on gray matter integrity in Veterans specifically becomes increasingly relevant when we consider that the areas affected by CP in studies of civilians seem to overlap with areas affected by other deployment-related conditions like PTSD and mTBI. Studies from various groups have shown a decrease in the thickness and volume of gray matter in the insular and cingulate cortices of individuals suffering from PTSD (Bryant et al., 2008; Corbo et al., 2005, 2014; Dickie et al., 2012; Eckart et al., 2011; Geuze et al., 2008; Herringa et al., 2012; Kasai et al., 2008; Kitayama et al., 2006; Lindemer et al., 2013; Woodward et al., 2006). Other studies have investigated the impact of TBI, which has also been shown to co-occur with CP, on gray matter integrity and have found some evidence of regional and global atrophy (Bergeson et al., 2004; Celik et al., 2005; Gale et al., 1995; Levine et al., 2008; Strangman et al., 2010; Yount et al., 2002). These findings mirror evidence from clinical studies showing possible interaction between psychological symptoms and pain sensations. This in turn raises an important question: if a history of CP is associated with a greater severity of PTSD and mTBI symptoms, and if these clinical conditions in isolation have been shown to affect overlapping cortical gray matter, is there a difference in the relationship between gray matter integrity and deployment-related conditions in Veterans with versus without a history of CP?

In the current study, we took advantage of a well-characterized sample of Veterans from Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND). We elected to approach CP in Veterans from an ecological perspective to study two primary questions.

- First, based on the studies showing gray matter thickness and volume decreases in individuals with CP, we investigated if Veterans with CP would also present similarly decreased gray matter integrity measured using cortical thickness, while controlling statistically for other symptoms (e.g. PTSD, Depression, mTBIs). Based on previous studies, we hypothesized that Veterans with CP would evidence decreased thickness in the ACC, insula and dorso-lateral prefrontal cortex.
- Second we investigated whether the presence of CP modifies the association between gray matter integrity and severity of trauma, as well as clinical symptoms of PTSD. Based on studies showing greater PTSD severity in Veterans with CP, we hypothesized that Veterans with CP would present stronger association between cortical thickness and PTSD severity/Combat Exposure than Veterans without CP.

2. Materials and methods

2.1. Subjects

157 Veterans were recruited from the Translational Research Center for TBI and Stress Disorders (TRACTS), a VA Rehabilitation Research and Development, National Center for TBI Research (NRC) of the Veterans Affairs Boston Healthcare System (VABHS). Participants were from all branches of the military and from the greater New England area. The TRACTS cohort has been describe elsewhere (Lippa et al., 2015) and is considered representative of the current population of OEF/OIF/OND Veterans. In short, inclusion criteria included service to OEF, OIF, and/or OND. Veterans were excluded from enrolling in TRACTS if they had any of the following: history of seizures; prior serious medical illness; current active suicidal and/or homicidal ideation, intent, or plan requiring crisis intervention; current DSM-IV-TR diagnosis of bipolar disorder, schizophrenia or other psychotic disorder (except psychosis NOS due to trauma-related hallucinations); or cognitive disorder due to general medical condition other than TBI. We further excluded participants that presented any contraindication for the Magnetic Resonance Imaging (MRI; e.g. pacemaker, metal implants not compatible with MRI, pregnancy) or that reported a history of moderate to severe TBI, as this may have affected both pain levels and gray matter integrity.

The subjects were grouped based on a documented history of CP. History of chronic pain (CP, $N=54$) was determined based on one of three sources (Powell et al., 2015): (1) the presence of a diagnosis in the Centralized Patient Record System (CPRS); (2) if they mentioned pain lasting for longer than 3 months during their clinical interview or; (3) if they were referred to the VABHS Pain Clinic after consensus meeting between clinical psychologist of TRACTS. The control group ($N=103$) included participants of the TRACTS cohort that were negative for a history of chronic pain based on the three criteria mentioned above. Ratings of current acute pain (in the last 30 days) were not an exclusion criterion. For the current study, groups were formed based on a history of CP, independent of current diagnosis, which could not be reliably collected. Participants of both groups were deployed and control participants were not excluded based on a history of PTSD diagnosis, depression or lifetime history of mTBI.

Because initial analyses revealed significant differences on clinical scales between the CP and control group, we matched each participant of the CP group with an individual in the Control group to reduce differences between groups. Criteria for pairing were a PTSD severity (based on total CAPS score) of ± 5 and age ± 5 years. If more than one participant in the control group matched a case in the CP group, inclusion of the final match was done using randomized selection (selecting one control participant using "random" function in Microsoft Excel). Because of our criteria, 5 participants of the CP group were excluded because no match