Lifetime PTSD and geriatric depression symptomatology relate to altered dorsomedial frontal and amygdala morphometry

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A R T I C L E   I N F O

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A B S T R A C T

Posttraumatic stress disorder (PTSD) affects a large portion of combat deployed Veterans. Moreover, many individuals also suffer from comorbid late life depression (geriatric depression; GD). While a great deal of research has begun to characterize the morphometric features of PTSD and depression individually, few studies have investigated the interacting effect of these two disorders, specifically in a Veteran population. The current study used cortical and subcortical surface-based morphometry (SBM) in combination with psychological assessments of PTSD and GD symptom severity to examine morphometric alterations in Vietnam War Veterans. Our results indicate that increased GD severity, PTSD symptomatology, and their interaction, was related to decreased grey matter volume (GMV) in the left dorsomedial prefrontal cortex (dmPFC). Furthermore, increased symptomatology in the PTSD subscales of reexperiencing and hyperarousal were additionally found to be related to decreased GMV in this same dmPFC region. Subcortically, the interacting effect between PTSD and GD was also significantly related to regional shape variation in the left amygdala. These results suggest that morphometry of cortical (dmPFC) and non-neocortical regions (amygdala) putatively underlying emotional reactivity and the emotional components of memory is altered in PTSD and GD.

1. Introduction

Exposure to trauma can engender the development of posttraumatic stress disorder (PTSD), a disorder which affects a significant percentage (e.g., 10–30%) of deployed combat Veterans (i.e., Vietnam War, Operation Enduring Freedom and Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND); (Dolan et al., 2012; Hoge et al., 2004). Hallmark symptoms of PTSD include flashbacks, emotional numbing, avoidance behaviors, increased anger, arousal and hypervigilance. These symptoms can cause significant distress, impair daily functioning, and persist for years or even decades (Hoge et al., 2006; Weiner et al., 2014). Findings from a Vietnam Veteran Readjustment Study conducted by Schlenger et al. (1992) reported that over 15% of Veterans still suffered from PTSD fifteen or more years after military service (Schlenger et al., 1992).

Neuroimaging research of individuals with PTSD consistently reports anatomical abnormalities in the hippocampal/amygdalar complex, when compared to control subjects (Karl et al., 2006), including reductions in grey matter volume (GMV; Bremner, 2007; Depue et al., 2014). Other frequently replicated morphological findings include reduced GMV of the ventromedial prefrontal cortex (vmPFC), including the subgenual anterior cingulate cortex (sgACC), regions putatively responsible for regulation of the amygdalar/hippocampal complex (Kitayama et al., 2005; Rauch et al., 2003; Smith, 2005). The traditional neurocircuity model of PTSD suggests a hypoactivation of the aforementioned medial PFC (mPFC), in relation to hyperactivation of the amygdala and abnormal functioning of the hippocampus (Rauch et al., 2006). More recent functional studies have been less conclusive, reporting both hyper- and hypoactivation of these regions (Lanius et al., 2001; Shin et al., 2004) however, this may in part be due to variations in experimental paradigms employed. Despite these inconsistencies, it is generally agreed upon that alterations in this vmPFC/sgACC—amygdalar/hippocampal complex pathway are associated with decreased regulatory control over response to fearful and threatening...
Furthermore, PTSD is associated with increased risk of comorbid conditions. A national survey of individuals with lifetime PTSD reported over 80% suffered from at least one other psychiatric disorder, with major depression being among the most prevalent (Kessler et al., 1995). Major depression is a mood disorder characterized by recurring depressive episodes with symptoms such as low mood, anhedonia, lack of motivation, and reduced sleep, appetite and libido (Fitzgerald et al., 2008). While numerous neuroimaging studies have been conducted on depression, the culmination of which is outside of the scope of this paper, it is noteworthy that parallel to the anatomical findings of PTSD, meta-analyses have revealed that individuals with depression also exhibit decreases in mPFC and hippocampal volume, compared to healthy controls (Campbell et al., 2004; Koolschijn et al., 2009). In fact, these are two of the most commonly reported findings in neuroimaging research conducted on depression. 

Taken together, a singular diagnosis of PTSD or GD share similar abnormalities in neuroanatomical substrates, however, less is known about the comorbidity of PTSD and depression, and specifically the comorbidity with late life depression (i.e. geriatric depression; GD). Therefore, in the present study we aimed to increase our understanding of the neural correlates underlying PTSD, GD, and principally their comorbid symptomatology in Vietnam Veterans. We employed neuroimaging surface-based morphometric (SBM) analysis of cortical grey matter and subcortical regional shape and volume, in combination with neuropsychological assessments of PTSD and GD, including separate symptom clusters of PTSD, as well as duration and recurrence of depression. We hypothesized that increases in both PTSD and GD symptomatology would be associated with decreases in cortical thickness or volume in regions involved in emotional reactivity, its regulation, and emotional components of memory (i.e., amygdala, hippocampus, mPFC). In doing so, we aim to provide a greater understanding of the cortical and subcortical morphometric features related to PTSD, GD, and their comorbidity in a Vietnam Veteran population.

2. Methods

Data used in the preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). Launched in 2003, ADNI is an ongoing, longitudinal, multicenter study supported by the National Institutes of Health (NIH) and private industry sponsors, and is led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI is to validate and standardize the use of neuroimaging, in combination with other neuropsychological assessments, as biomarkers to measure the progression of mild cognitive impairment (MCI) and early Alzheimer’s disease (AD). The Vietnam Veterans ADNI Project (ADNI DOD) is the newest addition to ADNI and aims to study the effects of TBI and PTSD on AD using imaging and biomarkers. The ADNI database is available to all qualified researchers and has currently supported over 300 publications (Weiner et al., 2012). For up to date information, see www.adni.info.org.

2.1. Participants

A total of 88 right-handed male combat-exposed Vietnam War Veterans were selected from the ADNI DOD database for inclusion in this study, based on availability of imaging data for each participant and completion of all neuropsychological assessments of interest (mean age 69.1, SD 4.7 years). For initial inclusion in the ADNI DOD database, the San Francisco VA Medical Center (SFVAMC) used military and Veterans Affairs Compensations and Pension records to identify Vietnam War Veterans with evidence of ongoing PTSD and comparable Veteran controls matched for age, education. Potential participants were initially screened via telephone using an adapted version of the Eight-item Informant Interview to Differentiate Age and Dementia (AD8; Galvin et al., 2005), in addition to some of the questions from the Clinical Dementia Rating (CDR), as a first pass to screen out individuals with mild cognitive impairment (MCI) or dementia.

After an initial telephone screening, all eligible subjects underwent a clinical psychological interview using the Structured Diagnostic Interview SCID-I for DSM IV-TR, and the Clinician Administered PTSD Scale (CAPS) by telephone, conducted by the PTSD Core at the SFVAMC. For inclusion in the PTSD group (N = 42, mean age 67.6, SD 4.0 years), subjects had to meet DSM-IV-TR criteria for current/chronic PTSD (Spitzer et al., 1992), and have a minimum current Clinician Administered PTSD Scale (CAPS) score of 50 related to a Vietnam War associated trauma, and no history of head trauma. Control subjects (N = 46, mean age 70.5, SD 5.0 years) could not have any documented or self-report history of head trauma, traumatic brain injury (TBI), history of PTSD or current PTSD, or a CAPS score > 30.

All participants had a Mini Mental State Exam (MMSE) score between 24 and 30, and a Clinical Dementia Rating (CDR) of 0, to further support that these participants were not cognitively impaired. Any participants meeting criteria for mild cognitive impairment or dementia at any of the previous checkpoints were excluded from the ADNI DOD study. Potentially confounding factors were also used as exclusion criteria, including a history of psychotic or neurologic illness, a recent history of alcohol or substance abuse, or the presence of metal implants that have been determined to be unsafe for magnetic resonance imaging (MRI).

Participants who were deemed eligible to participate and lived within 150 miles of an approved Department of Defense (DOD) ADNI clinic, were referred to their local site for imaging studies and additional neuropsychological assessments including: the Geriatric Depression Scale (GDS) which assesses depressive symptoms in old age, and the Combat Exposure Scales (CES) which measures wartime stressors experienced by combatants. For a comprehensive list of inclusion/exclusion criteria, in addition to all neuropsychological assessments given, please see the ADNI DOD procedure and protocol manuals.

Data from all individuals in our sample were included in the surface-based morphometry analyses, although eight participants were excluded from the FIRST analyses due to unsatisfactory subcortical segmentation (PTSD group N = 35, Veteran controls N = 45).

2.2. Neuropsychological assessments

2.2.1. Clinician Administered PTSD Scale (CAPS)

The CAPS is the gold standard in PTSD assessment. It is a 30-item structured interview that can be used to make current and lifetime diagnoses of PTSD (Blake et al., 1995). The CAPS can be used as both a dichotomous (present/absent) diagnostic measure using DSM IV-TR guidelines, or as a continuous measure of PTSD symptom severity (Blake et al., 1995). Five severity score ranges have been proposed for interpreting CAPS total severity: 0–19 = asymptomatic/few symptoms, 20–39 = mild PTSD/subthreshold, 40–59 = moderate PTSD/threshold, 60–79 = severe PTSD symptomatology, ≥ 80 = extreme PTSD symptomatology (Weathers et al., 2001). In addition, CAPS measures the frequency and intensity of PTSD related symptoms, and can be scored to focus on the severity rating within each of the three PTSD symptom clusters: reexperiencing, avoidance and numbing, and hyperarousal (Weathers et al., 2001).

2.2.2. Geriatric Depression Scale (GDS)

The Geriatric Depression Scale (short form) is a self-report scale designed to identify symptoms of depression in the elderly. The scale consists of 15 questions to which the subject is asked to answer yes or no based on how they have felt over the past week. One point is given for each answer indicating depressive tendencies. The GDS may be used with healthy individuals as well as mild to moderately cognitively impaired older adults and has been found to have 92% sensitivity and 99% specificity against diagnostic criteria. A score of 0–4 is considered normal, 5–8 suggests mild depression, 9–11 indicates moderate...
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