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Full-length Article

Current posttraumatic stress disorder and exaggerated threat sensitivity associated with elevated inflammation in the Mind Your Heart Study

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ABSTRACT

Objective: Elevated inflammation has been repeatedly observed in posttraumatic stress disorder (PTSD), and it may drive the development of both psychiatric symptoms and physical comorbidities. However, it is not clear if elevated inflammation is a feature of both remitted and current PTSD, and little is known about relationships between specific clusters of PTSD symptoms and inflammation. Exaggerated threat sensitivity, as indexed by threat reactivity and avoidance of perceived threats, may be particularly closely associated with inflammation.

Methods: We assessed PTSD symptoms and threat sensitivity using the Clinician Administered PTSD Scale in 735 Veterans Affairs patients (35% current PTSD; 16% remitted PTSD) who participated in the Mind Your Heart Study (mean age = 59 ± 11; 94% male). High sensitivity C-reactive protein (hsCRP), white blood cell count (WBC), and fibrinogen were used as indices of inflammation. Analysis of covariance models with planned contrasts were used to examine differences in inflammation by PTSD status, adjusting for age, sex, race, kidney function and socioeconomic status.

Results: Individuals with current PTSD had significantly higher hsCRP and WBC than patients with no history of PTSD, but there were no significant differences in inflammatory markers between those with remitted versus no history of PTSD. Within patients with current PTSD, higher threat reactivity was independently associated with higher hsCRP ($\beta = 0.16$, $p = 0.01$) and WBC count ($\beta = 0.24$, <0.001), and higher effortful avoidance was associated with higher fibrinogen ($\beta = 0.13$, $p = 0.04$).

Conclusion: Our data indicate that elevated inflammation may be a feature of current, but not remitted, PTSD. Within patients with PTSD, higher threat reactivity was also associated with elevated inflammation. A better understanding of the relationship between threat sensitivity and inflammation may inform interventions for patients with PTSD.

1. Introduction

Posttraumatic stress disorder (PTSD) is a common and disabling disorder that affects approximately 7–10% of the general population and 10–30% of military veterans (Boscarino, 2006; Dohrenwend et al., 2007; Seal et al., 2008). Increased systemic inflammation may contribute to PTSD-related increased risk for chronic physical diseases, including cardiovascular (Cohen et al., 2009a), neurodegenerative (Yaffe et al., 2010), and autoimmune disorders (Boscarino, 2004; Boscarino et al., 2010; O'Donovan et al., 2015b). Accumulating evidence indicates that inflammation may also provoke psychiatric symptoms seen in PTSD (Dantzer et al., 2008; Raison et al., 2013; Slavich and Irwin, 2014). In line with this hypothesis, several studies have reported that PTSD is associated with elevated inflammation. A better understanding of the association between PTSD and inflammation could lead to the development of novel therapies to improve mental and physical health in trauma-exposed individuals.

Multiple studies have found that individuals with current PTSD display elevated levels of systemic inflammatory markers, including C-reactive protein (CRP), white blood cell count (WBC), and fibrinogen (Boscarino and Chang, 1999; Heath et al., 2013; Hoge et al., 2009; Plantinga et al., 2013; Spitzer et al., 2010; Vaccarino et al., 2010; Vidovic et al., 2010, 2007; von Kanel et al., 2006, 2007). Several lines of evidence suggest that the observed

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relationship between PTSD and inflammation could be bidirectional. First, traumatic stress exposure itself as well as PTSD symptoms could promote inflammation via the stress response. Studies have demonstrated that inflammation is increased chronically in individuals exposed to traumatic stress and acutely in response to standardized psychosocial stressors (Black, 2002; Cohen et al., 2007; Danese et al., 2007; Dekaris et al., 1993; O'Donovan et al., 2012; Steptoe et al., 2007). Second, inflammation may be causally involved in the development of PTSD symptoms. Animal models and experimental human studies demonstrate that inflammatory activity can evoke symptoms analogous to some of the core symptoms of PTSD (Chen et al., 2013; Dantzer et al., 2008; Engler et al., 2011; Inagaki et al., 2012; Raison et al., 2013). There is also some evidence that elevated inflammation, as indexed by higher levels of the inflammatory marker C-reactive protein (CRP), increases risk for the development of PTSD following trauma exposure (Eraly et al., 2014).

To date, most research examining the relationship between PTSD and inflammation has compared individuals with current PTSD to those without current PTSD. Less attention has been paid to examining inflammation in those with a past history of PTSD that has gone into remission. Among the small studies that have examined inflammation in those with remitted PTSD, one indicated lower levels of some inflammatory markers in individuals with remitted compared to no history of PTSD (Kawamura et al., 2001), and one indicated that individuals with remitted PTSD had levels of inflammatory markers similar to those of controls and significantly lower than those of individuals with current PTSD (Gill et al., 2013). Thus, it remains unclear if elevated inflammation is a correlate of current PTSD symptomatology or a stable factor indexing either vulnerability to develop PTSD or a lingering consequence of PTSD.

Although most studies have observed elevated inflammation in PTSD, there are some notable exceptions finding either similar or even lower levels of inflammatory proteins in individuals with current PTSD compared to healthy controls (O'Donovan et al., 2015a; Sondergaard et al., 2004; von Kanel et al., 2010). These inconsistent findings in the literature may be because PTSD is a heterogeneous disorder and elevated inflammation is likely to be present in only a subset of patients with PTSD. For example, evidence from studies with small sample sizes indicates that some categories of PTSD symptoms may be more strongly associated with elevated inflammation than others, though results have been mixed (Ironson et al., 1997; von Kanel et al., 2006). In general, these studies have used standard re-experiencing, avoidance, and hyperarousal clusters of symptoms from the Diagnostic and Statistical Manual-IV to classify PTSD symptoms (APA, 2000). While these categorizations are highly useful in the clinical setting, they may be less useful in the effort to uncover the underlying biological basis of specific domains of dysfunction because symptoms in a single category may not arise from a common underlying pattern of dysfunction (Insel et al., 2010). Among the various domains identified in the National Institute of Mental Health's Research Domain Criteria (RDoC), threat sensitivity is particularly important in the context of the relationship between PTSD and inflammation. Patients with PTSD differ in their levels of threat sensitivity, and both threat reactivity and avoidance have been linked with elevated inflammation in clinical and animal research studies (Chen et al., 2013; Engler et al., 2011; Inagaki et al., 2012; Michopoulos et al., 2015). However, little is known about the relationship between threat sensitivity and inflammation in individuals with PTSD.

In the present study, we assessed inflammation as indexed by hsCRP, WBC, and fibrinogen in a large sample of Veterans Affairs (VA) patients with current, remitted, or no history of PTSD. To our knowledge, our sample of 735 patients is the first to include large numbers of patients with both current and remitted PTSD in a single study. In addition, we explored associations of these inflammatory markers with threat reactivity and avoidance in individuals with current PTSD. No prior studies have attempted to examine if PTSD symptoms specifically related to threat sensitivity are associated with inflammation. Given that adverse health behaviors may play a key role in the relationship between PTSD and inflammation (O'Connor and Irwin, 2010; Spoormaker and Montgomery, 2008; Talbot et al., 2013; Zen et al., 2012), we also examined BMI, smoking, physical inactivity, sleep quality, and alcohol use as potential contributors to the association of PTSD and threat sensitivity with inflammation. We hypothesized that current, but not remitted PTSD would be associated with elevated inflammation, and that exaggerated threat reactivity and avoidance would be associated with elevated levels of inflammatory markers in individuals with current PTSD.

2. Methods

2.1. Participants

The Mind Your Heart Study is a prospective cohort study designed to examine the effects of PTSD on health outcomes in VA patients. Between February 2008 and June 2010, data were gathered from adult patients recruited from outpatient clinics affiliated with two Bay Area Departments of VA Medical Centers: the San Francisco VA Medical Center and the VA Palo Alto Health Care System, California. Patients who planned on leaving the area within three years or who did not have stable mailing or contact information for follow-up were excluded during the recruitment process. Because the study involved an exercise treadmill test (see Turner et al., 2013 for details), potential participants were also excluded if they had a myocardial infarction in the prior six months or if they were unable to walk one block. If participants reported symptoms of acute illness, their appointment was rescheduled. Targeted mailings were used to oversample for people with current and remitted PTSD. Overall, 1020 patients were recruited and assessed for eligibility. Of these, 104 were ineligible and 170 were eligible but did not complete enrollment, leaving 746 patients who enrolled in the study. Eleven patients were excluded from the present analyses because they did not have complete data on their PTSD assessments or because the supervising psychologist had concerns regarding the accuracy of their PTSD diagnoses. Thus, the sample for the present study includes 735 VA patients. The study was approved by the Committee on Human Research at the University of California, San Francisco, and all participants provided written informed consent.

2.2. Psychiatric diagnoses

The Clinician-Administered PTSD Scale (CAPS), a structured interview measure that corresponds to DSM-IV criteria for PTSD, was used to assess PTSD symptoms. The CAPS has excellent convergent and discriminant validity, diagnostic utility and inter-item and inter-rater reliability and is highly sensitive to clinical change, based on a review of over 200 studies (Weathers et al., 2001). Interviewers assessed symptoms experienced in the previous month for current PTSD, and symptoms experienced during the worst episode associated with the subject's self-identified worst traumatic event for lifetime PTSD. We used the standard DSM-IV scoring rule to determine symptom positivity, requiring a score of at least 1 for frequency and 2 for intensity (Weathers et al., 2001). In addition to full PTSD, we assessed partial PTSD, which has been associated with significant impairment in health and functioning (Marshall et al., 2001; Sayer et al., 2010). Though there are multiple definitions of partial PTSD, we chose a