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# Proinflammatory milieu in combat-related PTSD is independent of depression and early life stress

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ABSTRACT

*Background:* Chronic inflammation may be involved in combat-related post-traumatic stress disorder (PTSD) and may help explain comorbid physical diseases. However, the extent to which combat exposure *per se*, depression, or early life trauma, all of which are associated with combat PTSD, may confound the relationship between PTSD and inflammation is unclear.
*Methods:* We quantified interleukin (IL)-6, IL-1β, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and C-reactive protein (CRP) in 51 combat-exposed males with PTSD and 51 combat-exposed males without PTSD, and assessed PTSD and depression severity as well as history of early life trauma. To decrease the possibility of Type I errors, we summed standardized scores of IL-1β, IL-6, TNFα, IFNγ and CRP into a total "pro-inflammatory score". PTSD symptom severity was assessed with the Clinician Administered PTSD Scale (CAPS) rating scale.
*Results:* Subjects with PTSD had significantly higher pro-inflammatory scores compared to combat-exposed subjects without PTSD ($p = 0.006$), and even after controlling for early life trauma, depression diagnosis and severity, body mass index, ethnicity, education, asthma/allergies, time since combat and the use of possibly confounding medications ($p = 0.002$). Within the PTSD group, the pro-inflammatory score was not significantly correlated with depressive symptom severity, CAPS total score, or with the number of early life traumas.
*Conclusions:* Combat-related PTSD in males is associated with higher levels of pro-inflammatory cytokines, even after accounting for depression and early life trauma. These results, from one of the largest studies of inflammatory cytokines in PTSD to date, suggest that immune activation may be a core element of PTSD pathophysiology more so than a signature of combat exposure alone.
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## 1. Introduction

Post-traumatic stress disorder (PTSD) is a prevalent condition imposing a considerable burden on the individual and on society (Hidalgo and Davidson, 2000; Kessler et al., 1995). Among U.S. soldiers returning from the Iraq and Afghanistan conflicts ("Operation Iraqi Freedom" and "Operation Enduring Freedom"), PTSD prevalence is approximately 18% and 12%, respectively (Hoge et al., 2004), and much higher in veterans being treated in Veterans Affairs healthcare settings (Seal et al., 2009). PTSD may develop

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after an event that involves threatened death or serious injury, or threat to the physical integrity of oneself or others. The core symptoms include flashbacks, startle reactions, nightmares, insomnia, intrusive thoughts and images, and avoidance of reminders of the trauma (American Psychiatric Association, 1995). Robust biological correlates of PTSD diagnosis, risk and prognosis are lacking, and pharmacological treatments are in many cases inadequate (Stein et al., 2006), which calls for further investigations of the biological mechanisms underlying PTSD. Moreover, individuals with PTSD are at a substantially increased risk of developing various medical illnesses, e.g. those associated with the immune, cardiovascular, musculoskeletal, gastrointestinal and central nervous systems (Frayne et al., 2011), but the biological underpinnings of this are unknown.

Several studies have reported significantly higher mean concentrations of various pro-inflammatory cytokines in serum (Guo et al., 2012; Hoge et al., 2009; Maes et al., 1999; Spitzer et al., 2010; Spivak et al., 1997; Tucker et al., 2004) and in cerebrospinal fluid (CSF) (Baker et al., 2001) of individuals with PTSD, although not all studies are in agreement (Bonne et al., 2011; Kawamura et al., 2001; McCanlies et al., 2011). Possible sources of discrepancy across studies include small sample sizes and the failure to account for the potential confounding effects of comorbid Major Depressive Disorder (MDD) and early life trauma, all of which are common in combat-related PTSD (Breslau et al., 1999; Gros et al., 2012; Kessler et al., 1995), and some of which may, themselves, be accompanied by elevations of pro-inflammatory cytokines (Lindqvist et al., 2009; Schiepers et al., 2005; Slopen et al., 2013). To the best of our knowledge, no prior studies have included a control group comprised entirely of combat-exposed individuals as a means to account for the potential confounding effect of combat exposure *per se* on cytokine levels, and only three studies have included controls that have experienced trauma of some sort (Kawamura et al., 2001; Spitzer et al., 2010; Tucker et al., 2004). This is important since lifetime trauma exposure has been associated with inflammation even after adjusting for psychiatric disorder such as PTSD and MDD (O'Donovan et al., 2012).

This highlights the importance of adequately powered studies with comprehensive diagnostics and combat-exposed controls, in order to determine whether PTSD, once potential confounders are factored out, is associated with increased immune activation. Further, older age, certain medical disorders and many medications commonly prescribed to individuals with PTSD (e.g., antidepressants, anti-inflammatories, statins) affect the biomarkers under investigation. The objectives of this study were to determine if young combat-exposed men with PTSD display higher levels of pro-inflammatory cytokines, compared to age-matched combat-exposed men without PTSD, and to determine if this relationship is significant after covarying for MDD diagnosis, early life traumatic events, physical illnesses, and medications, as well as to determine whether higher pro-inflammatory cytokine levels are associated with more severe PTSD symptomatology.

## 2. Material and methods

### 2.1. Ethical statement

The Institutional Review Boards of Mt. Sinai School of Medicine (New York, NY), the James J. Peters Veterans Administration Medical Center (Bronx, New York), New York University Medical Center (New York, NY), and the University of California, San Francisco, Medical Center (San Francisco, CA) approved this study. Study participants gave written and informed consent to participate. The study was conducted in accordance with the provisions of the Helsinki Declaration.

### 2.2. Recruitment procedures

One hundred and four Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) veterans were recruited by New York University (NYU) and Mt. Sinai/James J. Peters Veterans Administration (MSSM/JJPVAMC). NYU recruited 59 subjects, and 45 were recruited at MSSM/JJPVAMC. Subjects were recruited from the Mental Health Services of the Manhattan, Bronx and Brooklyn Veterans Affairs Medical Centers, other regional VA medical centers, Veterans Service Organizations, National Guard, reservist agencies and organizations and from the general community. Recruitment methods included flyers, in-person presentations, media advertisements, internet postings (e.g. Craigslist) and referral from clinicians. Participants were compensated for their participation.

Criteria for inclusion were: (a) PTSD subjects were positive for current war zone-related PTSD of at least 3 months duration, as indexed by the DSM-IV and the Clinician Administered PTSD Scale (CAPS) (Blake et al., 1990) criteria with CAPS score >40; (b) control subjects had also served in war zones but were negative for lifetime PTSD and had a current CAPS score <20; (c) age between 20 and 60; (d) males; and (e) proficient in the English language. The following exclusion criteria were employed for all subjects: (a) history of alcohol dependence within the past 8 months; (b) history of drug abuse or dependence (except nicotine dependence) within the past year; (c) lifetime history of any psychiatric disorder with psychotic features, bipolar disorder, or obsessive-compulsive disorder; (d) those who were currently exposed to recurrent trauma or have been exposed to a traumatic event within the past 3 months; (e) subjects with prominent suicidal or homicidal ideation; (f) neurologic disorder or systemic illness affecting central nervous system function; (g) anemia, recent blood donation in the past 2 months; (i) subjects who were not stable for 2 + months on psychiatric medication, anticonvulsants, antihypertensive medication or sympathomimetic medication; (j) subjects who were classified with a moderate or severe traumatic brain injury (TBI) on the Ohio State University TBI Identification Method––Short Form; and finally (*k*) subjects who experienced loss of consciousness for greater than 10 min. Mean (±SD) time between combat and blood draw was 55.5 (±28.4) months for PTSD subjects and 40.5 (±25.3) months for controls ($t = -2.8$, $df = 100$, $p = 0.006$). All study participants (PTSD subjects and controls) experienced combat-theater traumas described in criterion A of DSM-IV PTSD diagnostic criteria but only the PTSD subjects fulfilled the remaining necessary criteria for PTSD. The CAPS was used to assess the presence versus absence of a DSM-IV diagnosis of PTSD related to combat trauma exposure and to assess symptom severity of the combat-related PTSD. The SCID PTSD module was used to determine whether participants had ever met DSM-IV diagnostic criteria for PTSD related to a non-combat traumatic exposure. Veterans in the control group were excluded from participation if they had ever met criteria for PTSD to any traumatic exposure.

### 2.3. Study participants

Fifty-two combat-exposed male subjects with PTSD and 52 combat-exposed psychiatrically healthy controls who were age-matched, were recruited for the study. Twenty-seven of the PTSD subjects, but none of the controls, were diagnosed with concurrent MDD. Structured Clinical Interview for DSM-IV disorders (First, 1997) were conducted by Doctoral level psychologists, and were audio recorded and calibrated weekly with a senior clinician in the PTSD program. There were no significant between-group differences in site of deployment (PTSD subjects: 73% Iraq only, 8% Afghanistan only, 16% both Iraq and Afghanistan, 4% other locations; Controls 69% Iraq only, 18% Afghanistan only, 14% both

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