



An investigation of vago-regulatory and health-behavior accounts for increased inflammation in posttraumatic stress disorder



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ABSTRACT

Objective: Posttraumatic stress disorder (PTSD) has been linked to chronic inflammation, a condition that poses a risk for cardiovascular disease. Attenuated vagal activity has been proposed as a potential mediator of PTSD and inflammation, although associated behavioral health risks—namely cigarette smoking and alcohol dependence—might also account for that link.

Methods: Inflammation was quantified by fasting serum concentrations of C-reactive protein (CRP), tumor necrosis factor (TNF)- α , interleukin (IL)-10, and thymus- and activation-regulated chemokine (TARC)/CCL17 collected from 85 participants with PTSD and 82 without PTSD. Latent variable modeling was used to assess the relationship between PTSD symptom severity and inflammation along with potential mediators vagal activity (respiratory sinus arrhythmia; RSA), smoking status, and lifetime alcohol dependence.

Results: PTSD symptom severity was associated with increased inflammation ($\beta = .18, p = .02$). However, this association was reduced in models that adjusted for RSA, smoking status, and lifetime alcohol dependence. Independent mediation effects were deemed significant via bootstrapping analyses. Together, RSA, smoking status, and lifetime alcohol dependence accounted for 95% of the effect of PTSD symptom severity on inflammation.

Conclusion: Although RSA accounted for a modest proportion of the association between posttraumatic stress and pro-inflammatory responses, behavioral factors—specifically cigarette smoking and alcohol dependence—proved to be larger mediators. The benefits of PTSD treatment may be enhanced by additional interventions aimed at modifying these health behaviors.

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1. Introduction

Posttraumatic stress disorder (PTSD) is a chronic condition precipitated by exposure to a traumatic event. It is characterized by intrusive re-experiencing of the traumatic event, avoidance of stimuli evocative of that event, negative alterations in cognitions and mood, and hyperarousal [1]. PTSD also frequently conveys physical health symptoms, perhaps most notably cardiovascular disease [2]. For instance, PTSD has been prospectively associated with coronary heart disease [3] and cardiovascular mortality [4]. Although the pathway from posttraumatic stress to cardiovascular risk is not well understood, emerging evidence suggests that inflammation may play a key role [5].

Under conditions of heightened threat or stress, the sympathetic nervous system activates a “fight or flight” response, characterized by

increased cardiovascular and metabolic activity. The immune system also responds in kind, presumably to stave off infections resulting from injuries sustained during such fight or flight. The initial immune response is fast and generalized, during which numbers of phagocytes, including neutrophils and macrophages, are mobilized. Macrophages in turn release pro-inflammatory communication factors (cytokines), including interleukin (IL)-1, IL-6, C-reactive protein (CRP), and tumor necrosis factor alpha (TNF- α), which cause fever and inflammation while contributing to healing. A second, more specific immune response is also initiated in which lymphocytes become activated upon attaching to chemically matched pathogens, thereby initiating lymphocyte expansion and cytokine release. These cytokines include the pro-inflammatory IL-2 and interferon gamma (IFN- γ) as well as the anti-inflammatory IL-4, IL-10, and thymus- and activation-regulated chemokine (TARC/CCL17), which regulate lymphocyte activity.

Over the past two decades, a number of studies have found that psychological stress is associated with elevated cytokine levels, reflecting heightened inflammation [6]. For instance, several studies have found

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that exposure to trauma in childhood [7–9] and in adulthood [10] is subsequently predictive of increased inflammation. One study even found that increased cytokine levels post-trauma were predictive of later development of PTSD [11]. In fact, with the exception of a few studies [12–15], PTSD is generally associated with increased cytokine levels [16–22], even above and beyond the effect of trauma exposure [23,24].

The link between PTSD and inflammation is complex but may be partially explained by behavioral risk factors associated with PTSD [22]. For instance, individuals with PTSD are more likely than those without PTSD to smoke and do so heavily [25], be obese [26], and abuse alcohol [27]. Each of these risk factors is independently associated with inflammation [28–30]. Autonomic dysfunction may also partially account for the association between PTSD and inflammation. Individuals with PTSD exhibit suppressed heart-rate variability (HRV) [31–33], which is likely due to attenuated vagal regulation of sympathetic arousal [34]. Given the central role of the vagus nerve in inhibiting generalized immune response [35–37], vagal dysregulation has been proposed as a pathway by which PTSD is associated with chronic inflammation [38].

Although behavioral risk factors and depressed vagal activity have been suggested as potential mechanisms linking PTSD and inflammation, no research has verified this let alone compared their relative mediation effects. Thus, the purpose of the present study was to determine whether the association between PTSD symptom severity and inflammation is partially mediated by vagal activity, smoking status, and history of alcohol dependence, and, if so, which mediator accounts for the largest portion of that association. As such, fasting serum concentrations of CRP, TNF- α , IL-10, and TARC were assayed from a sample of young (i.e., < 40 years of age), largely trauma-exposed adults. Latent variable modeling was used to model inflammation via the four cytokines *en route* to testing three sets of hypotheses: 1) PTSD symptom severity is positively associated with inflammation; 2) PTSD symptom severity is associated with reduced vagal activity, greater smoking, and higher rates of lifetime alcohol dependence; and 3) vagal activity, smoking status, and lifetime alcohol dependence partially mediate the association between PTSD symptom severity and inflammation.

2. Material and methods

2.1. Participants

Participants were 167 young adults (18–39 years old; 80 women), including 63 U.S. military veterans, who were recruited via fliers displayed in hospital clinics and waiting rooms as well as online ads such as Craigslist to complete a study of the metabolic, cardiovascular, and neuroimmunological risk factors associated with trauma exposure. Criteria for exclusion from the study included presence of a) organic mental disorder, b) schizophrenia, c) bipolar I mixed state or bipolar II, d) lifetime PTSD without current PTSD, e) current substance abuse/dependence, f) current major depressive disorder (MDD) without PTSD, g) pregnancy, h) AIDS or HIV, and i) uncontrolled medical condition (e.g., liver failure). Eleven women using birth control and three participants using statins were additionally omitted from the present analysis in light of the potential effects of these drugs on cytokine levels. The study was approved by both the Durham Veterans Affairs and Duke University Medical Center Institutional Review Boards. All patients gave written informed consent before participation. Data were collected between August 2008 and September 2013. Previous findings from this sample include linkages between PTSD and orthostatic hypotension [39], decreased HRV [32], and dyslipidemia [40].

2.2. Measures

2.2.1. Posttraumatic stress disorder

PTSD status was assessed using the Clinician Administered PTSD Scale (CAPS) [41], based on DSM-IV criteria [42]. The 17-item structured

interview was administered by a licensed clinical psychologist or by a trainee under the direct supervision of a licensed clinical psychologist. Interrater reliability among interviewers was high (Fleiss' $k = .94$) across five training tapes. The CAPS interview has excellent reliability within multiple trauma populations and is widely accepted as the state-of-the-art method for PTSD assessment [43].

The 17-item self-report Davidson Trauma Scale (DTS) [44] was used to quantify PTSD symptom severity based on DSM-IV criteria. Each item measures the frequency (0, “not at all,” to 4, “everyday”) and intensity (0, “not at all distressing,” to 4, “extremely distressing”) of corresponding symptoms. Total symptom severity scores were calculated by summing frequency and intensity ratings across all items.

2.2.2. Vagal activity

One commonly used method for measuring vagal cardiac control, or activity, is via respiratory sinus arrhythmia (RSA) [45], which refers to the naturally occurring fluctuations in heart rate associated with breathing. To capture RSA, beat-by-beat blood pressure and heart rate data were measured continuously using the Finometer noninvasive blood-pressure monitor (Finapres Medical Systems, Amsterdam) under supine conditions. Following five minutes of calibration, one 5-minute file of continuous blood pressure and heart rate measurements was recorded for assessment of RSA while the participants breathed at their regular rate of breathing. Blood pressure waveforms were reviewed, and artifacts due to movement or abnormal heart beats removed and replaced by the pulse interval values from the preceding beat(s). The beat-by-beat systolic pressure and heart rate data were linearly interpolated and resampled at a frequency of 4 Hz in order to generate an equally spaced time series for the variables. A fast Fourier transform was then applied to the interpolated data after detrending and application of a Hanning filtering window. Power spectra were derived using the Welch algorithm, which ensemble averages successive periodograms [46]. The averaged spectrum was derived from the power spectra estimated from nine 60-s data segments, overlapping by half. For each 60-s segment, 256 points were analyzed, which included 240 sampled points with zero padding. Consistent with prior research [47–49], RSA was estimated from the R-R interval power summed across the high-frequency 0.13- to 0.50-Hz respiratory band. Raw RSA was log-transformed before analysis in order to normalize values.

2.2.3. Smoking status

Smoking status was operationalized based on participants' responses to the Fagerström Test for Nicotine Dependence [50]. Non-smokers were assigned a value 0; past—but not present—smokers, 1; current smokers who consume 10 or fewer cigarettes per day, 2; and current smokers who consume more than 10 cigarettes per day, 3.

2.2.4. Lifetime alcohol dependence

The Structured Clinical Interview for the DSM-IV (SCID) [51] was used to assess Axis I disorders, including lifetime alcohol dependence. Study interviewers completed an extensive training program involving the rating of seven video-recorded interviews. Interviewers additionally participated in biweekly reliability meetings and were supervised by licensed clinical psychologists. Interrater reliability among interviewers for Axis I diagnoses was high (Fleiss' $k = .96$).

2.2.5. Trauma exposure

Trauma exposure was measured using the Traumatic Life Events Questionnaire (TLEQ) [52], a self-report questionnaire that documents 23 distinct types of traumas including the time of their occurrence. For the purposes of this study, trauma exposure was operationalized as the number of years since one's initial exposure to a traumatic event resulting in feelings of fear, helplessness, and horror. Participants who were never exposed to such a trauma were assigned a trauma-exposure value of 0. We included years of trauma exposure, as opposed to number of types of traumatic experiences or childhood versus

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