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Cytokine production as a putative biological mechanism underlying stress sensitization in high combat exposed soldiers

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Summary
Objective: Combat stress exposed soldiers may respond to post-deployment stressful life events (SLE) with increases in symptoms of posttraumatic stress disorder (PTSD), consistent with a model of stress sensitization. Several lines of research point to sensitization as a model to describe the relations between exposure to traumatic events, subsequent SLE, and symptoms of PTSD. Based on previous findings we hypothesized that immune activation, measured as a high in vitro capacity of leukocytes to produce cytokines upon stimulation, underlies stress sensitization.
Methods: We assessed mitogen-induced cytokine production at 1 month, SLE at 1 year, and PTSD symptoms from 1 month up to 2 years post-deployment in soldiers returned from deployment to Afghanistan ($N = 693$). Exploratory structural equation modeling as well as latent growth models were applied.
Results: The data demonstrated significant three-way interaction effects of combat stress exposure, cytokine production, and post-deployment SLE on linear change in PTSD symptoms over the first 2 years following return from deployment. In soldiers reporting high combat stress

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exposure, both high mitogen-stimulated T-cell cytokine production and high innate cytokine production were associated with increases in PTSD symptoms in response to post-deployment SLE. In low combat stress exposed soldiers as well as those with low cytokine production, post-deployment SLE were not associated with increases in PTSD symptoms.
Conclusion: High stimulated T-cell and innate cytokine production may contribute to stress sensitization in recently deployed, high combat stress exposed soldiers. These findings suggest that detecting and eventually normalizing immune activation may potentially complement future strategies to prevent progression of PTSD symptoms following return from deployment.

1. Introduction

Exposure to traumatic stressors may increase an individual's reactivity to subsequent stressors, a process that has been termed stress sensitization (Antelman et al., 1980; Post and Weiss, 1998). Stress sensitization has been proposed by several authors to play a role in the development of symptoms of posttraumatic stress disorder (PTSD) after exposure to traumatic events (Antelman and Yehuda, 1994; McFarlane, 2010). Consistent with the stress sensitization hypothesis, prior exposure to traumatic life events has been found to sensitize a person to the impact of subsequent stressors (Bland et al., 1996; Breslau et al., 1999; Dougall et al., 2000; Kessler et al., 1995; King et al., 1996; Smith et al., 2008). A number of prospective studies (Grasso et al., 2012; Smid et al., 2012, 2013) have provided evidence for stress sensitization following exposure to traumatic events. In a study of Dutch soldiers (Smid et al., 2013), high combat stress exposure was found to be associated with sensitization to the effects of post-deployment stressors during the first year following return from deployment. Specifically, a steeper linear increase in PTSD symptoms post-deployment was predicted by more post-deployment stressors in high combat stress exposed soldiers, but not in a less combat stress exposed group. A protective effect of exposure to potentially traumatic events on subsequent stress reactivity, often termed stress inoculation, has been found in persons who were only mildly affected and who managed to cope successfully (Norris and Murrell, 1988; Parker et al., 2004; Seery et al., 2010). Sensitization has also been described in conjunction with kindling in PTSD (Post and Weiss, 1998). Sensitization refers to externally induced symptoms, e.g. flashbacks of traumatic events induced by a subsequent stressor, whereas kindling refers to spontaneous symptoms, e.g. flashbacks occurring in the absence of an apparent cue. It has been suggested that kindling may follow sensitization, e.g., when flashbacks are triggered by progressively less severe stressors over time and eventually occur spontaneously (Post and Weiss, 1998).

Exposure to potentially traumatic events as well as symptoms of PTSD have been linked with alterations in the functioning of the immune system (Pace and Heim, 2011). Indeed, an accumulating body of evidence suggests that cytokines subserve processes such as learning and memory, that are involved in the pathogenesis of PTSD (Baker et al., 2012). A number of studies have investigated the capacity of peripheral leukocytes of individuals with PTSD symptoms to produce cytokines after in vitro stimulation (de Kloet et al., 2007; Gill et al., 2008; Gola et al., 2013; Kawamura et al., 2001; Rohleder et al., 2004; Woods et al., 2005). Increased (Gill et al., 2008; Rohleder et al., 2004; Woods et al., 2005), unchanged (Gola et al., 2013), and decreased (de Kloet et al., 2007) mitogen-induced pro-inflammatory cytokine production in individuals with PTSD symptoms compared to non-traumatized controls has been found, as well as decreased production in individuals with a past history of PTSD (Kawamura et al., 2001). Increased non-stimulated production of pro-inflammatory cytokines in PTSD patients compared with controls has also been reported (Gola et al., 2013). Thus, the predominant finding amongst three studies appears to be that cytokine production is increased in PTSD as compared to non-traumatized controls. The discrepancy in study findings may be explained by differences in sample characteristics, such as the type of trauma experienced (e.g. childhood vs. adult trauma), time elapsed since the trauma, comorbid disorders, PTSD symptom severity, and possibly exposure to SLE after the traumatic event.

In a previous study from our group (Van Zuiden et al., 2011b), high stimulated pre-deployment T-cell cytokine production predicted development of depressive symptoms in response to military deployment, as measured 6 months after return. This study used exploratory structural equation modeling (ESEM), an advanced statistical technique, to diminish redundancy in cytokine data stemming from functional overlap. Using this exploratory technique, functionally distinct cytokine/chemokine factors originating from the innate and adaptive immune system were identified, specifically, T-cell cytokines, T-cell chemokines (including IL-6), and innate cytokines.

This same study (Van Zuiden et al., 2011b) reported an increase in stimulated T-cell cytokine production from pre-deployment to 6 months post-deployment, indicating that deployment to a combat-zone increases the capacity of T-cells to produce cytokines until at least 6 months after return. Conversely, stimulated T-cell chemokine/IL-6 production as well as innate cytokine production after stimulation with Lipopolysaccharide decreased during this interval. Extrapolating from these results, it may be hypothesized that this increased T-cell cytokine production capacity in response to deployment could confer an increased risk for development of depressive symptoms after confrontation with new stressors (Van Zuiden et al., 2011b). Thus, increased T-cell cytokine production may be involved in the previously observed stress sensitization in high combat stress exposed soldiers. This is in line with previously reported evidence (Hayley et al., 2003) that the pro-inflammatory cytokine TNF-α sensitizes neural systems,