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# Symptom severity predicts degree of T cell activation in adult women following childhood maltreatment

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**Abstract**

Although depression is often associated with a reduction in cellular immune responses, other types of emotional disturbance and psychopathology can activate certain aspects of immunity. Activation markers on T cells, in particular, have been found to be elevated in post-traumatic stress states. However, little is known about the relationship between the severity of PTSD symptoms and the degree of change in T cell phenotypes, or about the potential role of neuroendocrine factors in mediating the association. Twenty-four women with a history of sexual trauma during childhood, including 11 who met diagnostic criteria for PTSD, were compared to 12 age-matched, healthy women without a history of maltreatment. The women provided fasted blood samples for enumeration of cell subsets by immunofluorescence and 24-h urine samples for analysis of catecholamine and cortisol levels. The percent of T cells expressing CD45RA, an early activation marker, was higher in the PTSD diagnosed women, and the levels correlated positively with intrusive symptoms and negatively with avoidant symptoms. These alterations in cell surface markers did not appear to be mediated by norepinephrine (NE) or cortisol, making them a distinctive and independent biomarker of arousal and disturbance in PTSD.
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*Keywords:* Memory T cell; Childhood sexual abuse; NE; Post-traumatic stress disorder

## 1. Introduction

Post-traumatic stress disorder (PTSD) is an anxiety disorder characterized by intrusive recall of a prior trauma, active avoidance of reminders of the traumatic events, and heightened autonomic arousal (American Psychiatric Association, 1994). Affected individuals vacillate between periods of high arousal, accompanied by flashbacks or unwanted memories, and behavioral efforts to avoid reminders of the original trauma (Horowitz, 1976; van der Kolk, 1987). By its very nature, PTSD is experienced as a dynamic and highly individualized disorder. Two patients with similar overall symptom severity may present quite differently: one showing a preponderance of intrusive symptoms, while another manifests more avoidant symptoms. Thus, some have argued that a greater appreciation of the individual variation in these psychological features is critical for understanding the PTSD patient (Foa et al., 1995). We hypothesized further that variability in presentation might shed light on the neuroendocrine and immune correlates of PTSD.

Many researchers have reported that individuals with PTSD have a unique neuroendocrine profile, which is often characterized by elevated norepinephrine (NE) in conjunction with low or slightly below normal cortisol levels, although some also have found elevated cortisol (Carrion et al., 2002; Heim et al., 2001; Mason et al., 1988; Oquendo et al., 2003; Yehuda et al., 1994). A growing literature also indicates that a chronic disturbance of immune regulation can accompany PTSD, including abnormal numbers and types of T lymphocytes in circulation. For example, Woods

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et al. (2005a) found that PTSD symptoms induced by interpersonal violence were correlated with the absolute number of $CD4^+$ and $CD8^+$ cells in a symptom-specific manner. Intrusive symptoms were positively associated with $CD4^+$ numbers, but not $CD8^+$ cells, whereas avoidance was positively linked to both $CD4^+$ and $CD8^+$ cells.

In addition, a history of childhood sexual abuse may continue to affect T cell number and activity in adulthood via the persistence of PTSD symptoms. The severity of the PTSD appears to drive the relationship between an abuse history and the increased production of IFN-γ by T cells (Woods et al., 2005a). Moreover, a study of 10 adult women with a current diagnosis of PTSD secondary to childhood sexual trauma found an elevated ratio of $CD45RO^+/CD45RA^+$ lymphocytes, suggestive of chronic immune activation (Wilson et al., 1999). In general, these immune findings concur with other surveys of larger samples, which indicated that a history of childhood trauma was associated with higher lymphocyte counts later in adulthood (Surtees et al., 2003). One possible functional significance for these phenotypic changes was suggested by the fact that women with PTSD related to childhood sexual abuse evince larger delayed type hypersensitivity responses (DTH) (Altemus et al., 2003), a cutaneous reaction involving both T regulatory and effector cells (Li et al., 1994; Werfel et al., 1995).

The number of T cells in circulation has been determined in several aroused and traumatized populations both with and without PTSD diagnoses (Ironson et al., 2007). For example, an elevated CD4/CD8 cell ratio—both at baseline and following a laboratory challenge—was seen in women experiencing post-traumatic stress symptoms related to a diagnosis of cancer in their children (Glover et al., 2005). In contrast, following sustained exposure to an environmental disaster, both $CD4^+$ and $CD8^+$ lymphocytes were reduced in a community survey after Hurricane Andrew when compared to normative values in the laboratory control subjects (Ironson et al., 1997). Immune evaluations of Vietnam veterans with a current PTSD diagnosis have yielded more mixed results, with some investigators reporting lower lymphocyte counts and a tendency for reduced $CD4^+$ and $CD8^+$ cell percentages (Boscarino and Chang, 1999), while others failed to replicate those results (Laudenslager et al., 1996). Given the mixed results, it seemed of value to continue investigating how these immune alterations generalize across different types of trauma, and especially to consider the relationship to the profile of symptoms.

There have actually been very few studies that simultaneously examined diagnostic category, symptom presentation, and the mediating role of neuroendocrine factors on the immune disturbance. Our primary aim was to examine the relative contribution of intrusive thought, distress, and avoidance, important components of PTSD in women with a history of childhood maltreatment (Antelman et al., 1997; Horowitz, 1976), and to replicate the evidence for chronic immune activation (Wilson et al., 1999). A secondary goal was to examine the potential neuroendocrine mediation. Intrusion was hypothesized *a priori* to be an important negative predictor on the basis of its effects on number of natural killer cells (NK) (Ironson et al., 1997) and expression of IL-2 receptors on lymphocytes (La Via et al., 1996). It was also important to determine whether concurrent changes in neuroendocrine activity, specifically, abnormal levels of NE or cortisol, accounted for the aberrant lymphocyte profile. Other conditions that increase autonomic activity, including vigorous exercise and preeclampsia during pregnancy, lead to increases in T cell activation markers, including naïve $CD45RA^+$, memory $CD45RO^+$, and the transitional $CD45RA^+CD45RO^+$ cells (Chaiworapongsa et al., 2002; Chavance et al., 1993; Gabriel et al., 1993; Hong et al., 2004; Kryzywkowski et al., 2001; Sondergaard et al., 2000). A mediating role for cortisol has also been implicated in Vietnam veterans with PTSD, who were found to have high levels of glucocorticoid receptors (GR) on their lymphocytes, suggestive of an upregulation in response to chronically low cortisol (Yehuda et al., 1991). However, attempts to replicate that result after the Bosnian conflict revealed that Croatian combat veterans with PTSD actually had the opposite profile with elevated cortisol levels and reduced GR receptors on lymphocytes (Gotovac et al., 2003). These inconsistencies may be explained by recent research indicating that both hormone and immune effects vary with the type of the trauma, the passage of time since the traumatic event, as well as the severity of symptoms (Kawamura et al., 2001; Yehuda, 2003). It seemed imperative to determine if symptom presentation and severity helped to explain the degree of lymphocyte activation, and to verify if the immune changes were dependent upon abnormal neuroendocrine activity.

## 2. Methods

### 2.1. Participants

Thirty-six women with or without a history of childhood maltreatment participated in this study. Participants were recruited through advertisements placed in local newspapers or announcements in specialized treatment centers. The study was described in all advertisements as a study of "the effects of women's early experiences on adult mental and physical health". Phone interviews were conducted to screen for eligibility. The newspaper advertisements for control and abused participants indicated we were looking for women who were between 18 and 40 years of age, menstruating regularly, non-medicated and willing to provide blood and urine samples. When recruiting non-abused controls, the callers were informed that we sought to evaluate women who had never experienced any unwanted sexual contact prior to 18 years of age either within or outside of the home. The only difference in the advertisement for controls was the absence of the words "sexual abuse survivors" in the title. Both advertisements also indicated that an examination by medical staff would be included. After being screened as a likely candidate meeting criteria, all participants completed the PTSD Symptom Scale, a validated and standardized interview that assesses 17 DSM-III-R symptoms of PTSD (Foa et al., 1993, 1995).

A total of 72 women were initially screened (mean age = 30.3, SD = 6.4 years). Half were not included because of rigorous exclusion criteria, including the presence of any current physical disease or use of any medication with immune-modulating effects, as determined by self-report and a review of the medical interview by a physician (MC). All