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The effect of trauma-focused therapy on the altered T cell distribution in individuals with PTSD: Evidence from a randomized controlled trial

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ABSTRACT

Posttraumatic stress disorder (PTSD) is associated with a reduced ratio of naïve cytotoxic T lymphocytes, an increased ratio of memory cytotoxic T lymphocytes, and a reduced proportion of FoxP3$^+$ regulatory T lymphocytes. This study investigated whether these immunological alterations are reversible through an evidence-based psychotherapeutic treatment. Therefore, 34 individuals with PTSD were randomly assigned to either a treatment condition of 12 sessions narrative exposure therapy (NET) or a waitlist control (WLC) group. PTSD symptoms were significantly reduced in the NET group, but not in the WLC group, four months post-therapy (effect size: Hedges' $g = -1.61$). One year after therapy, PTSD symptoms were improved even further in the NET group compared to baseline (Hedges' $g = -1.96$). This symptom improvement was mirrored in an increase in the originally reduced proportion of regulatory T cells (T_{regs}) in the NET group at the one-year follow-up, when comparing subgroups matched for baseline T_{reg} numbers. However, no changes were found for the initially reduced proportion of CD45RA$^+$CCR7$^+$ naïve T lymphocytes. In conclusion, NET was effective in reducing trauma-related PTSD symptoms and had a positive effect on the proportion of T_{regs} cells, thus demonstrating an effect of psychotherapy on an immunological level. Yet, the shift in the proportion of naïve and memory T lymphocytes in individuals with PTSD, discussed in the literature as a correlate of premature immunosenescence, was not reversible and thus might render these patients permanently more susceptible to infectious diseases.

1. Introduction

The probability of developing posttraumatic stress disorder (PTSD) after psychological trauma increases with the number of traumatic event types experienced (Neuner et al., 2004a; Kolassa et al., 2010). Likewise, a dose–response effect of trauma exposure during childhood has been demonstrated for the development of physical health problems (Felitti et al., 1998) and impaired brain development (Teicher et al., 2012). Furthermore, an increased risk for somatic diseases like chronic pain, cancer, cardiovascular, respiratory, gastrointestinal, and autoimmune diseases has been reported for individuals with PTSD (Boscarino, 2004; Boscarino et al., 2010; Sareen et al., 2007), where the poor physical health found in individuals with PTSD might be moderated by altered immune functions and inflammatory processes (Von Känel et al., 2007; Pace and Heim, 2011; Spitzer et al., 2010).

However, linking PTSD to alterations of bulk T cell populations, representing a major branch of adaptive immunity, has been controversial: Whereas the number of circulating CD8$^+$ cytotoxic T cells in individuals with PTSD has been found to be mostly lower (Ironson et al., 1997; Kawamura et al., 2001; Sommershof et al.,

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2009) or unchanged (Altemus et al., 2006; Laudenslager et al., 1998; Vidović et al., 2007; Wilson et al., 1999), the number of circulating $CD3^+$ T lymphocytes or $CD4^+$ T helper cells has been found to be lower, unchanged or even higher (Ironson et al., 1997; Laudenslager et al., 1998; Boscarino and Chang, 1999; Wilson et al., 1999; Kawamura et al., 2001; Boscarino, 2004; Vidović et al., 2007; Sommershof et al., 2009). As peripheral T lymphocytes consist of a range of functionally different subpopulations, one reason for these inconsistent findings might be that changes in PTSD might be specific to certain T lymphocyte activation and differentiation states. Sommershof et al. (2009) investigated this further differentiation of $CD4^+$ T helper and $CD8^+$ cytotoxic T cells in naïve, memory and effector cells, applying a differentiation model of T cells defined by changes in the expression of the lineage markers CD45RA and CCR7 (Hamann et al., 1999; Sallusto et al., 1999). They found a decreased ratio of ($CD45RA^+CCR7^+$) naïve $CD8^+$ T cells and an increased proportion of ($CD45RA^-$) memory $CD8^+$ T cells in individuals with PTSD (Sommershof et al., 2009). As a shrinking repertoire of naïve T cells may correlate with an enhanced susceptibility to infectious diseases (Fagnoni et al., 2000; Shen et al., 1999), this reduction in naïve T cells represents a possible explanation for the enhanced risk of infectious diseases in individuals with PTSD (Sommershof et al., 2009). Furthermore, Sommershof et al. (2009) observed a 50% decrease in the proportion of $CD4^+CD25^+FoxP3^+$ regulatory T cells (T_{reg}) in individuals with PTSD. T_{reg} cells are critical for maintaining balance in the immune system, regulating the immune response, and preventing autoimmune diseases (Vignali et al., 2008). Decreased counts of $CD4^+CD25^+FOXP3^+$ T_{reg} cells have been associated with autoimmune diseases like diabetes, multiple sclerosis, rheumatoid arthritis, psoriasis, anemia and eczema (Bennett et al., 2001; Buckner, 2010; Wildin et al., 2002), conditions for which individuals with PTSD show an increased risk (Boscarino, 2004; Boscarino et al., 2010; Weisberg et al., 2002).

Given the considerable prevalence of traumatic stress, and in particular the high prevalence of PTSD in populations affected by conflict, terror and combat (Neuner et al., 2004a; Neuner and Elbert, 2007), a highly relevant question in the context of traumatic stress and physical disease is: Can effective treatment reverse the effects of traumatic stress not only on a psychological but also on an immunological level?

Trauma-focused psychotherapeutic interventions may effectively reduce trauma-related mental suffering in individuals with PTSD (Ehlers et al., 2010; Cloitre, 2009; Kleim et al., 2012; Seidler and Wagner, 2006), and, in individuals with PTSD with comorbid borderline personality disorder (Bohus et al., 2013) or comorbid substance abuse (van Dam et al., 2013). Moreover, it was demonstrated that successful psychotherapeutic treatment also significantly reduced cough, diarrhea, and fever (Neuner et al., 2008).

Yet, to our knowledge no study investigated the effect of psychotherapy on T lymphocyte distribution in individuals with PTSD. So far, the impact of psychological interventions on T lymphocyte populations has mainly been examined in patients with cancer and human immunodeficiency virus (HIV), yielding mixed results. There are studies reporting a stabilization of $CD4^+$ T lymphocytes after psychotherapeutic interventions (Creswell et al., 2009; Petrie et al., 2004; Sherman et al., 2000); however, $CD4^+$ and $CD8^+$ T lymphocytes were not affected in other studies (Antoni et al., 2006; Carrico et al., 2005; Hosaka et al., 2000).

Furthermore, we know that effective psychotherapy with Narrative Exposure Therapy (NET) can reverse the increased level of DNA strand breaks observed in individuals with PTSD compared to controls (Morath et al., in press). NET is a trauma-focused treatment approach for PTSD, developed for survivors of war and torture (Schauer et al., 2011a). Its efficacy has been proven in a number of randomized controlled trials in post-conflict regions (Ertl et al., 2011; Neuner et al., 2004b) and in Europe (Hensel-Dittmann et al., 2011; Robjant and Fazel, 2010).

The present study has two aims: 1) to extend the findings by Sommershof et al. (2009) in a larger sample of individuals with PTSD, trauma-exposed non-PTSD subjects and non-exposed controls and 2) to investigate whether the altered T cell distribution in individuals with PTSD can be reversed by psychotherapeutic treatment with NET. Individuals with PTSD were investigated before treatment and four and 12 months after the end of therapy and T cell differentiation subsets were analyzed. We hypothesized that the NET treatment group would show an increase in the proportions of $CD45RA^+CCR7^+$ naïve $CD8^+$ as well as in the proportion of $CD4^+CD25^+FOXP3^+$ T_{reg} cells.

2. Methods

2.1. Participants

Thirty-four individuals with PTSD and 43 non-PTSD controls were recruited through the Center of Excellence for Psychotraumatology, University of Konstanz, and public advertisements. Sixteen subjects with PTSD and 27 controls were also participants in a previous study by Sommershof et al. (2009). After the initial screening, individuals with PTSD (age 16–47 years) – refugees (13 Africa, 21 Middle East) with a history of war and torture experiences – were randomly assigned to either a treatment (NET group: $n = 17$) or a waitlist control condition (WLC group: $n = 17$). The non-PTSD control group (age 16–50 years) consisted of refugees and immigrants (9 Africa, 13 Balkan, 21 Middle East) without PTSD and varying traumatic load (0–9 traumatic event types). As the number of traumatic events experienced influences T cell distribution in a cumulative way (Sommershof et al., 2009), we further divided the control group into a group with substantial trauma exposure (*trauma-exposed*, $n = 24$) and a control group with no or little trauma exposure (*non-trauma-exposed*, $n = 19$) by median split of a traumatic load index.[2]

Exclusion criteria were acute infections or chronic somatic illnesses (e.g., HIV, osteoarthrosis, autoimmune diseases) and glucocorticoid medication. Non-trauma-exposed control group subjects were also excluded if they met the criteria for any mental disorder according to DSM-IV or reported taking psychotropic medication. Individuals with PTSD and trauma-exposed controls were excluded if they met the criteria for comorbid alcohol or substance abuse and dependence or a current or past history of a psychosis according to DSM-IV. The inflammation load between the time points of assessment was documented, and no severe illnesses were reported in between.

Individuals with PTSD showed no significant group differences from trauma-exposed and non-trauma-exposed controls with respect to age and smoking behavior, but groups differed significantly with respect to gender and intake of psychotropic medication (Table 1). Moreover, individuals with PTSD had experienced significantly more different traumatic event types (event list of the Clinician-Administered PTSD Scale [CAPS], Blake et al., 1995), significantly more war and torture events (Vivo checklist, Schauer et al., 2011b), and showed higher symptom scores in the CAPS, the Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960) and the screening for somatoform symptoms (SOMS-7; Rief and

[2] Traumatic load index = [(number of traumatic event types on the CAPS event list/items on the CAPS event list) + (number of war experiences on the vivo checklist/items on the war checklist) + (number of torture experiences on the vivo checklist/items on the torture checklist)].