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# Serum levels of interleukins IL-6 and IL-10 in individuals with posttraumatic stress disorder in a population-based sample

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ABSTRACT

To evaluate the serum levels of IL-6 and IL-10 anti-inflammatory interleukins in individuals with post-traumatic stress disorder (PTSD) in a population-based study. This is a paired study nested in a cross-sectional population-based study. All individuals who presented PTSD and did not present major depressive disorder, diagnostic by interview–Mini International Neuropsychiatric Interview were selected. From these, 41 healthy controls were matched by sex and age. Serum levels of IL-6 and IL-10 were measured by the ELISA, using commercial kits. The group of individuals with PTSD showed a significant increase in the serum levels of IL-6 and IL-10. Our results suggest that individuals with PTSD may present an activation of the immune system, which may lead to neuroinflammation.

## 1. Introduction

Post Traumatic Stress Disorder (PTSD) is a debilitating condition imposing a considerable burden on the individual and on society. Epidemiology studies report a lifetime prevalence of PTSD of approximately 8% in general population (Perkonigg et al., 2000). PTSD is more common in young adults, because they are more likely to be exposed to precipitating situations (Javidi and Yadollahie, 2012).

Currently, DSM-V described 20 typical symptoms of PTSD and are classified according to four dimensions (re-evaluation (Criterion A); avoidance/avoidance (Criterion B); persistent negative changes in cognitions and mood (Criterion C); increased excitability (Criterion D)). Regarding duration, PTSD can be categorized into two types: acute – symptoms persist for less than three months; and chronic – symptoms persist for three months or longer. There is also PTSD called delayed onset, which refers to a condition in which the onset of the illness occurs at least six months after the traumatic event (Javidi and Yadollahie, 2012).

PTSD may develop after traumatic event, such as threatened death or serious injury, or threat to the physical integrity of oneself or others (Lindqvist et al., 2014). It is well establish in literature that PTSD is associated with significant co-morbidities including major depression, substance and alcohol abuse, suicide, reduced life expectancy, as well as disability in daily activities, and increased health care utilization (El Khoury-Malhame et al., 2011; Norrholm et al., 2011).

In recent years, studies have shown the association between inflammatory system and pathophysiology of psychiatric diseases, included PTSD (Guo et al., 2012; Hoge et al., 2009; Michopoulos et al., 2017; Spitzer, 2014; Tucker et al., 2004). Studies with animal models have shown that immunobrain communications are closely interrelated. Thus, immune mediators such as interleukin 1 (IL-1), interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) are able to cross the blood-brain barrier, and this is one way in which peripheral immune reactivity may have impacts on the central nervous system (CNS) (Haroon et al., 2012). This peripheral inflammation results in a concomitant increase in the number of activated microglia and levels of inflammatory mediators of IL-1, IL-6 and TNF-α in the hippocampus and in anxiety behaviors (Yang et al., 2016).

Immune signaling contributes to the regulation of the hypothalamic-pituitary-adrenal (HPA) axis and other neurobiological processes

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that modulate behavior in the exposure to traumatic and stressful events (Haroon et al., 2012). In this same way, Tursich et al. (2014), in a recent meta-analysis, showed that individuals with PTSD have an increased concentration of IL-1 β, IL-6, TNF and PCR. However, IL-10 levels did not present statistical differences. Although studies have shown that PTSD is associated with increases in biochemical markers there is also evidence to suggest that there is no relationship between PTSD and increased inflammation, mainly IL-6 and IL-10 (Bersani et al., 2016; Guo et al., 2012; Lindqvist et al., 2014; Maes et al., 2009; Newton et al., 2014; Oganesyan et al., 2009; Passos et al., 2015; Smith, 2012; Song et al., 2007; von Kanel et al., 2007). Our hypothesis is that serum levels of IL-6 and IL-10 may be elevated in individuals with PTSD due to inflammatory activation caused in response to stress.

Thus, the aim of the study was to evaluate the serum levels of IL-6 pro-inflammatory interleukins and IL-10 anti-inflammatory interleukins in individuals with current PTSD in a population-based study.

## 2. Methods

### 2.1. Sample

This is a case-control study nested in a population-based one, of people aged 18–35, involving 2348 participants living in the city of Pelotas, (Brasil), between June 2011 and October 2012. Sample selection was performed by clusters, considering the census division of the city (Pelotas) in 2010 (IBGE—Instituto Brasileiro de Geografia e Estatística; http://www.ibge.gov.br). After identifying the subjects, they were invited to participate in the study and signed the informed consent form. This study was approved by the committee of ethics in research from the Catholic University of Pelotas (UCPEL), under Protocol number 15/2010.

### 2.2. Instruments

Socio-demographic and clinical issues as gender, ethnicity, age, tobacco use, weight and height and data on the use of psychoactive substances were collected through a semi-structured self-administered questionnaire. The Body Mass Index (BMI), calculated by the coefficient Body Weight (kg)/Height $(m)^2$. To evaluate alcohol use disorder, the participants also answered the CAGE questionnaire (Buchsbaum et al., 1992). Socio -economic evaluation was carried out using the IEN criteria (National Economic Index—Índice Econômico Nacional), which is based on the accumulation of material assets and on the schooling of the head of the household. These criteria generate a continuous variable which was presented in tertiles (Barros and Victora, 2005).

The diagnostic for psychiatric diagnostic assessments were measured by the Mini International Neuropsychiatric Interview (M.I.N.I), structured according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (Amorim, 2000).

Subjects who presented other psychiatric disorders, currently used illicit drugs (cocaine, cannabis, crack), psychiatric medications and anti-inflammatory drugs were excluded from this study (n = 965 individuals). Subsequently, individuals who presented a diagnosis of current posttraumatic stress disorder (PTSD) were selected (n = 41 individuals). Of these, 41 other individuals were randomly paired by sex and age, constituting a control group. (Fig. 1).

### 2.3. Biochemical analysis

For the biochemical analysis, 10 mL of blood were withdrawn from each subject after the interview by means of venipuncture into an anticoagulant-free vacuum tube, between 8:00 and 11:00 a.m. The blood was immediately centrifuged at4000 × g for 10 min, and serum was kept frozen at −80∘C until analysis. Serum levels of IL-6 and IL-10 were measured using a commercial immunoassay kit (DuoSetELISA Development, R & D Systems, Inc., USA) The biochemical analyst was blinded to samples. Serum IL-6 and IL-10 levels were expressed in pg/mL.

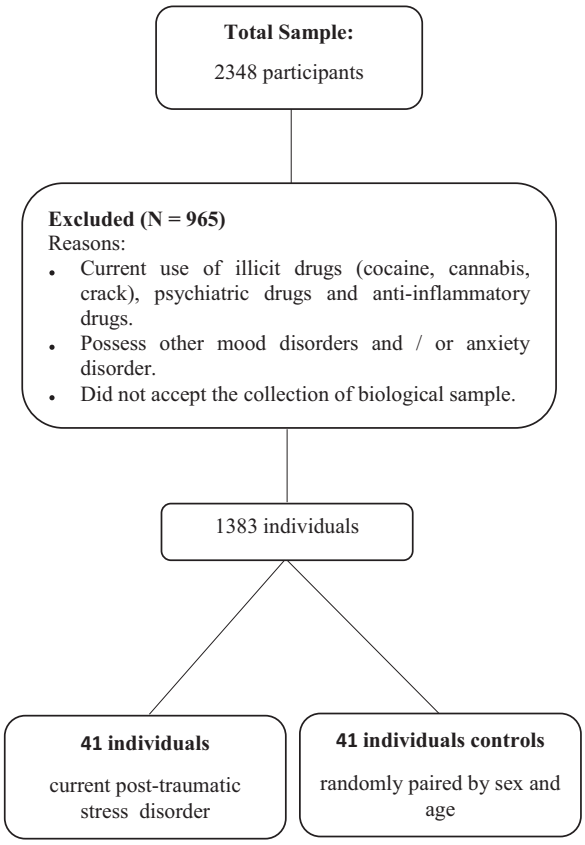


**Fig. 1.** Flow chart of the current PTSD group and control group.

### 2.4. Statistical analysis

Statistical analysis was performed with the Statistical Program for Social Sciences (SPSS) 21.0 and Graph Pad Prism 6.0. The descriptive analysis of the sample distribution of clinical and sociodemographic characteristics variables was carried out initially in relation to the groups with current PTSD and control group.

Independent variables (gender, ethnicity, age, economic level, years of schooling, tobacco use, alcohol abuse and BMI) and dependent variables (serum levels of IL-6 and IL-10) were considered in the study. In the bivariate analysis, the chi-square test was performed and, for the variables with normal distribution the student *t*-test.

Serum IL-6 and IL-10 levels had non-Gaussian distributions and are presented as median and interquartile range. Thus, the non-parametric Mann-Whitney test, the Spearman correlation test, and the Kruskal-Wallis test were performed. A linear regression analysis was applied to control for possible confounding factors with a p value ≤ 0.2 in the bivariate analysis. Serum levels of IL-6 and IL-10 did not present Gaussian distribution, only for linear regression analysis the data were logarithmically transformed. Results with p values ≤ 0.05 were considered statistically significant.

## 3. Results

The total sample consisted of 82 individuals: 41 with PTSD and 41 healthy control. Table 1 show the sociodemographic characteristics of the sample according to control and PTSD groups. Regarding socioeconomic level, in control group the majority of the individuals belonged to the high economic class (51.2%), while in the group of individuals with PTSD the majority belonged to low economic class