Alterations of the hypothalamus pituitary-axis on one hand and heightened rates of somatic diseases and mortality on the other hand are consistently found for PTSD and MDD patients. A possible link between these factors might be the immune system, in particular pro- and anti-inflammatory cytokines. A ‘low-grade inflammation’ in PTSD and MDD patients was found, whereas the influence of acute stress and the role of anti-inflammatory cytokines was rarely examined. In this study, 17 female PTSD patients participated in the Trier social stress test while serum cytokine levels (IL-6, IL-10) were assessed. Cytokine levels of PTSD patients were compared with levels of female depressive patients (n = 18) and female healthy controls (n = 18). Group differences were assessed using a 3 (group) x 8 (time: −15, −1, +1, +10, +20, +30, +45, +60 min) ANCOVA for repeated measures with baseline values as covariates. There was no group difference regarding IL-6 levels (p = 0.920) but PTSD patients showed significantly higher levels of IL-10 compared with depressive patients (p < 0.001, d = 0.16) and healthy controls (p = 0.001, d = 0.38). Under acute stress, PTSD patients did not show the widely found elevated IL-6 levels but showed an increase of anti-inflammatory IL-10. Therefore, acute stress seems to promote an imbalance of pro- and anti-inflammatory cytokine levels in PTSD and might indicate a hyperreactive immune response. This should be considered in future studies to further understand the role of the immune system as a link between stress response and somatic diseases.

**INTRODUCTION**

Patients suffering from mental disorders show higher rates of health care utilization, cardiac events, cardiac mortality and show higher mortality rates in general [1–4]. These effects are still present when controlling for other risk factors such as smoking history, socioeconomic status, Body Mass Index or somatic conditions such as hypertension [1, 3]. Posttraumatic stress disorder (PTSD) and major depressive disorder (MDD) are among the most common mental disorders with 6–9% of the European and American population suffering from PTSD and 12–15% suffering from depression [5]. Both are associated with a range of different somatic diseases such as cardiovascular, respiratory, gastrointestinal and autoimmune diseases [1, 4, 6, 7]. In general, female MDD and PTSD patients showed a 4-fold higher mortality risk compared with individuals not suffering from mental disorders even after controlling for other risk factors [4].

These findings emphasize the possibility of a direct association between psychological and somatic diseases. A possible explanation for these findings is an alteration of the hypothalamus pituitary adrenal-axis (HPA-axis) of PTSD and MDD patients which can in turn influence the immune system via cytokines [8].

Cytokines, a family of proteins mediating immune responses to injury, infection or other organismal stress, are associated with inflammatory diseases such as cardiovascular diseases, cancer, pulmonary disease or autoimmune disorders [8, 9]. An activation of the HPA-axis because of stress leads to a secretion of corticotrophin-releasing factor (CRF) from the hypothalamus [10]. CRF stimulates the release of adreno-corticothrophic hormone (ACTH) and this in turn stimulates the release of glucocorticoids. Glucocorticoids are hormones which can inhibit inflammatory cytokines such as Interleukin (IL-) 6 by downregulating cytokine expression and increase production of anti-inflammatory cytokines such as IL-10 via T cells. Thereby, an immunoregulatory activity is possessed [10]. These mechanisms are supposed to be altered in mental disorders and might therefore lead to body states promoting the development of the mentioned somatic diseases. Though different studies investigated the reactivity of the HPA-axis and cytokine levels in different patient groups, the influence of acute stress on cytokine levels in PTSD and MDD patients still remains unclear.

By assessing cortisol levels, conclusions about the HPA-axis response can be drawn. In a standardized stress test, a blunted HPA-axis stress reactivity was found in female PTSD patients compared with healthy controls [11]. Also, in a meta-analysis, lower cortisol levels in plasma and serum of PTSD patients were found compared with healthy controls [12]. Regarding cortisol reactivity of MDD patients, they showed descriptively lower levels than healthy controls and significantly lower levels than PTSD patients [13]. In general, PTSD and MDD patients show altered cortisol responses to stressors [11–15].

These alterations of the HPA-axis could influence the immune response and in turn lead to more physical diseases in these conditions. They can in turn influence the immune system via cytokines [8]. However, these effects are still present when controlling for other risk factors such as smoking history, socioeconomic status, Body Mass Index or somatic conditions such as hypertension [3]. Posttraumatic stress disorder (PTSD) and major depressive disorder (MDD) are among the most common mental disorders with 6–9% of the European and American population suffering from PTSD and 12–15% suffering from depression [5]. Both are associated with a range of different somatic diseases such as cardiovascular, respiratory, gastrointestinal and autoimmune diseases [1, 4, 6, 7]. In general, female MDD and PTSD patients showed a 4-fold higher mortality risk compared with individuals not suffering from mental disorders even after controlling for other risk factors [4].
patient groups. In PTSD, higher levels of pro-inflammatory markers compared with healthy controls were found, leading to the assumption of a ‘low-grade inflammation’ in PTSD [8, 9, 16]. Also, in MDD patients elevated levels of pro-inflammatory cytokines such as IL-6 were found compared with healthy controls [17, 18]. Therefore, it is suggested that these inflammatory states in PTSD and MDD might be a psychobiological mediator between psychological and somatic diseases [14]. Nevertheless, the influence of acute stress on cytokine levels in PTSD and MDD and the relation of cytokine levels in these disorders was rarely examined.

In addition to the low number of studies assessing cytokine levels of these patients under acute stress, the role of inflammatory cytokines such as IL-1β or IL-6 are mainly investigated and the role of anti-inflammatory cytokines such as IL-10 tends to be neglected.

To further assess cytokine levels of PTSD and MDD patients under acute stress, we assessed IL-6 and IL-10 levels of these patients and of healthy controls during the Trier social stress test. Based on this, conclusions about the acute stress reaction of these patients compared with healthy controls can be drawn. Additionally, conclusions about the cytokine levels of PTSD patients in relation to levels of MDD patients can be drawn. With this approach this study provides further insights regarding the assumed HPA-immune interaction via cytokines.

METHODS
Study sample
Patient groups (PTSD, MDD) were recruited at the University Medical Center Carl Gustav Carus of the Technische Universität Dresden during the beginning of their inpatient treatment or treatment at the day clinic of the Clinic and Polyclinic for Psychotherapy and Psychosomatics. Healthy controls were recruited via announcements at the website of the clinic. Participants with fluent German language skills and age between 18 and 65 were included in the study. General exclusion criteria were a lifetime history of substance use disorder, psychotic or bipolar disorder, history of substance use disorder, psychotic or bipolar disorder, and MDD might be a psychobiological mediator between psychological and somatic diseases [14]. Nevertheless, the influence of acute stress on cytokine levels in PTSD and MDD and the relation of cytokine levels in these disorders was rarely examined.

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Figures 1 and 2 show mean values of IL-6 and IL-10 levels for the measurement points of the TSST of PTSD, MDD patients and healthy controls. Results of the repeated measures ANCOVA can be derived from Table 2. Comparing IL-6 values, there was a significant main effect for time ($F(3.94, 189.25) = 9.03, p < 0.001, \eta^2_p = 0.158$) but not for group ($F(2, 48) = 0.08, p = 0.920$). IL-10 levels showed significant main effects for time ($F(3.80, 182.20) = 4.88, p = 0.001, \eta^2_p = 0.092$), a significant main effect for group ($F(2, 48) = 15.22, p < 0.001, \eta^2_p = 0.388$) and a significant interaction for time x group ($F(7.59, 182.20) = 3.05, p = 0.004, \eta^2_p = 0.113$). Bonferroni-adjusted post hoc analysis revealed significant differences in IL-10 levels between PTSD and MDD patients ($0.38, p < 0.001$).

Table 1. Means, standard deviations of questionnaire data and differences between groups (ANOVA with Post hoc-tests, Bonferroni corrected).

|                  | PTSD        | MDD        | HC         | M-Diff PTSD-MDD ($d$) | M-Diff PTSD-HC ($d$) | M-Diff MDD-HC ($d$) |
|------------------|-------------|------------|------------|-----------------------|---------------------|--------------------|
|                  | Mean (SD)   | Mean (SD)  | Mean (SD)  |                       |                     |                    |
| GSI              | 41.75 (4.06)| 36.29 (4.27)| 28.72 (5.80)| 0.10** (1.31)         | 0.16** (2.59)       | 0.06* (1.49)       |
| IES-R: intrusion | 21.13 (11.36)| 6.07 (5.66)| 3.78 (4.49)| 14.92** (1.69)        | 17.22** (2.03)      | 2.29               |
| IES-R: avoidance | 17.50 (4.04)| 5.07 (6.01)| 3.44 (4.78)| 11.82** (2.41)        | 13.44** (3.17)      | 1.63               |
| IES-R: hyperarousal | 17.63 (9.13)| 3.42 (4.51)| 2.56 (3.88)| 14.57** (1.99)        | 15.44** (2.17)      | 0.87               |
| BDI-II           | 28.88 (7.97)| 13.57 (9.25)| 6.28 (6.12)| 14.70** (1.77)        | 23.87** (3.19)      | 9.17* (0.93)       |
| VAS              | 53.70 (7.36)| 50.36 (13.99)| 54.77 (11.85)| 3.35               | −1.07               | −4.42              |
| PASA             | −0.50       | −0.06      | −1.61      | −0.44                | 1.11                | 1.56               |
| Stress index     | (4.73)      | (3.84)     | (4.15)     |                      |                     |                    |

PTSD post traumatic stress disorder, MDD major depression disorder, HC healthy control, SD Standard deviations, M-Diff Mean difference, GSI Global Severity Index, IES-R impact of event scale, BDI-II Beck depression inventory, VAS visual analog scale, PASA primary appraisal secondary appraisal, $d$ effect size Cohen’s $d$.

*p < 0.01; **p < 0.001.
Patients and healthy controls (0.27, 0.001, 95%-CI [0.21; 0.55]; \( \text{d} = 0.38 \)). There was no significant difference between MDD patients and healthy controls (0.11, \( p = 0.214 \), 95%-CI [−0.04; 0.26]).

**DISCUSSION**

In this study levels of pro- and anti-inflammatory cytokines were assessed under acute stress in PTSD and MDD patients and were compared with healthy controls. There were no group differences regarding pro-inflammatory cytokines (IL-6) but PTSD patients showed higher levels of anti-inflammatory cytokines (IL-10) compared with MDD and healthy controls. There was no difference in IL-10 levels between MDD patients and healthy controls. The finding of no group differences of pro-inflammatory cytokines is in contrast to past studies showing elevated IL-6 levels and suggesting a ‘low-grade inflammation’ in PTSD and MDD [8, 9, 16–18, 31]. In contrast to the present study, these studies mainly assessed fluctuating or spontaneous IL-6 levels without the influence of an acute stressor, which could be one reason for the discrepancies. Acute stress could influence the immune response of PTSD patients in a way that anti-inflammatory IL-10 becomes more present than in healthy controls or MDD patients and not – as found when assessed spontaneously – pro-inflammatory IL-6. Nevertheless, past studies found elevated IL-6 levels in PTSD and MDD [14, 32] patients under acute stress, after the TSST. Other studies reported no difference between PTSD patients and healthy controls regarding IL-6 but did find differences regarding other pro-inflammatory cytokines such as IL-1β and Tumor necrosis factor (TNF) \( \alpha \) [33]. They assumed, that these elevated levels might be first steps of a pro-inflammatory cascade later resulting in elevated IL-6 levels. As we did not assess these parameters, we cannot support this assumption with our data.

Elevated levels of IL-10 in PTSD patients compared with healthy controls were also found in past studies when serum cytokine levels were assessed [34, 35]. Higher levels of IL-10 usually occur to reduce inflammatory processes by inhibiting the production of pro-inflammatory cytokines such as IL-6 and therefore protecting the individual from an increased pro-inflammatory state with negative somatic consequences [35, 36]. On the other hand, as described, IL-10 is released via T-cells distinguished in two subtypes: T helper lymphocytes 1 (Th1) and T helper lymphocytes 2 (Th2) both releasing different sets of cytokines [10, 37]. It is suggested that an imbalance of Th1 and Th2 can be triggered by stress and may in turn encourage and/or sustain different somatic diseases [37, 38]. For example, stress-induced Th1 suppression leads to a Th2-shift, an overproduction of IL-10 amongst others and may favor the development of different cancer types [37, 38].

Based on this, especially a hyperreactive immune response due to an imbalance of Th1/Th2 could play a crucial role in the development of somatic diseases. As shown, PTSD patients have higher rates of circulating T-cells compared with healthy controls, which might support this assumption and which could lead to a hyperreactive immune response [1]. One assumption could be, that PTSD patients in general may show a hyperreactive immune response with an imbalance of pro- and anti-inflammatory cytokines and that this imbalance depends on the current state in which the individual is (acute stress vs. spontaneous assessment). This assumption needs to be further investigated whereas especially acute stressors could play a major role in the immune response and a potentially associated hyperreactivity promoting somatic diseases. In contrast to the other two groups, IL-10 levels of the PTSD patients show an increase directly after the TSST, decreases quickly and then rises again continuously. As studies assessing IL-10 levels under acute stress are very rare, it is not clear if this is a typical pattern in PTSD patients. Subjective stress levels (PASA, VAS) do not provide an explanation for this IL-10 pattern. In contrast, MDD patients did not show elevated IL-10 levels compared with healthy controls, which is in line with past studies [31]. As MDD patients do not show any differences in cytokine levels compared with healthy controls, the specific role of the immune system under acute stress in MDD patients remains unclear. The results more hint to the conclusion that other mechanisms might play a more important role in linking MDD and alterations in the HPA-axis with somatic diseases. Nevertheless, as described above past studies did find elevated IL-6 levels in MDD [17, 18], emphasizing alterations of the immune system in this patient group. For further conclusions future studies need to assess pro- and anti-inflammatory cytokine levels of MDD patients under acute stress.

One limitation of our study is, that potentially influencing factors such as severity or type of trauma were not taken into account. Additionally, PTSD patients showed high comorbidity rates. 16 out of 17 PTSD patients also suffered from MDD and PTSD patients showed higher BDII-II scores than MDD patients. Nevertheless, PTSD patients usually also suffer from other psychological diseases which reduces the possibility to assess patients only suffering from PTSD and would affect the generalizability of the results. Additionally, results of questionnaires about subjective symptom burden regarding PTSD symptoms showed, that the group of PTSD patients showed more/severe symptoms of PTSD compared with MDD which justifies the differentiation of these groups. PTSD patients also showed higher general symptom burden (SCL-90-R) compared with MDD patients showing that PTSD patients in this study generally suffer from more/severe symptoms. Lindqvist et al. (2014) [39] also showed, that despite influencing factors such as comorbid depression or time since trauma, elevated pro-inflammatory cytokine levels could still be found though it was accounted for these factors. This study investigated two representatives of pro- (IL-6) and anti-inflammatory (IL-10) cytokines. To draw general conclusions about patterns of these cytokines in PTSD and MDD patients under acute stress, studies need to assess other pro- and anti-inflammatory cytokines.
stress, in future studies further cytokines need to be taken into account. As only female participants were investigated in this study, the generalizability of the results is reduced. As shown in past studies [40], there are gender differences in the immune response when individuals are under acute stress which emphasizes the necessity of investigating cytokine levels of both female and male PTSD and MDD patients under acute stress.

All in all, this study shows elevated anti-inflammatory cytokine levels in PTSD patients compared with MDD and healthy controls and no elevated levels of pro-inflammatory IL-6 in both patient groups compared with healthy controls. This finding might reflect a hyperreactive immune system in PTSD patients, which could lead to higher rates of somatic diseases and mortality in these patients. This assumption needs to be investigated in future studies wherein the influence of acute stress on cytokine levels should be taken into account.

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COMPETING INTERESTS
The authors declare no competing interests.

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