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Biomarkers in PTSD-susceptible and resistant veterans with war experience of more than ten years ago: FOCUS ON cortisol, thyroid hormones, testosterone and GABA

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ABSTRACT

In the present study we measured the concentrations of cortisol, thyroid hormones, testosterone, and GABA (gamma aminobutyric acid) in am blood plasma samples of combatants with an at least 10 year history of military psychological trauma (N = 74) divided in groups that either suffer from post-traumatic stress disorder (PTSD) (N = 37) or are resistant (N = 37) as well as in a control group without traumatic experience in the anamnesis, (N = 34). PTSD symptoms were assessed using the Clinician-Administered PTSD Scale (CAPS).

The results show that the am blood cortisol levels of individuals that were exposed to war zone experiences irrespective susceptibility for or resistance to PTSD were significantly higher than the values observed in the controls. Testosterone levels in PTSD patients differed neither from that observed in PTSD resistant nor control groups. In the resistant group testosterone levels were however significantly higher than in controls. The level of all thyroid hormones did not differ between the study groups. GABA level was significantly lower in the PTSD group compared with healthy controls. In the resistant group blood GABA levels were not significantly different from either PTSD patients or controls.

In conclusion, the current data show that cortisol and to some extent testosterone may serve as biomarker of war zone stress per se, even if trauma was experienced at least ten years before, rather than of only PTSD or resistance to PTSD. GABA, in contrast, can be considered a potential marker of the protracted nature of PTSD.

1. Introduction

The role of the hypothalamic-pituitary-adrenal (HPA) axis and its endproduct cortisol in the precipitation of posttraumatic stress disorder (PTSD), is well-documented [Yehuda \(2000\)](#); [Pitman \(2012\)](#) In veteran

PTSD patients, commonly hypocortisolism is measured for instance in e. g. the so-called ‘cortisol awakening response’, likely because of enhanced glucocorticoid feedback ([Wingenfeld et al., 2015](#); [Rhind et al., 2017](#); [Rauch et al., 2020](#)). However, the literature also presents data on significant increases in blood as well as hair cortisol levels of PTSD patients

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(Song et al., 2008; Steudte et al., 2011). According to some studies (Meewisse et al., 2007; Weems and Carrion, 2007), this inconsistency is due to the dependence of the cortisol level on the nature of the trauma, the time passed after the experienced trauma and susceptibility of patients with current and past PTSD to daily stressors. Nevertheless the role of cortisol and its receptors in memory consolidation of fear and anxiety is firmly established (de Quervain et al., 2017).

Although cortisol is important, it is not the only marker for PTSD. Currently, data on changes in the level of circulating thyroid hormones, testosterone, and GABA (gamma aminobutyric acid) of patients with PTSD are accumulating (Wang and Mason, 1999). In particular, the tri-iodothyronine level in respondents with PTSD associates positively with the number of traumatic events and additional hyperarousal (Karlovic et al., 2004).

Changes in the hypothalamic-pituitary-gonadal axis can also be connected to the development and decline of PTSD symptoms. Reijnen (2015) showed that the testosterone levels among soldiers were increased after deployment compared to pre-deployment levels. Although the testosterone levels did not differ between subjects with PTSD and healthy controls, reduced testosterone levels prior to deployment predicted the development of PTSD 1 and 2 years after deployment. Since testosterone has an anxiolytic effect (Hermans et al., 2006) and blocks the fear response to unconscious threats, the initially reduced level of this hormone may serve as a predisposing risk factor for the development of PTSD. In contrast, research by Mason et al. (1990) and Karlovic et al. (2012) reported elevated plasma testosterone levels in subjects with PTSD compared to a healthy control.

In addition to these hormones the blood level of some markers that are also a neurotransmitter in the brain, eg γ -aminobutyric acid (GABA) may also be PTSD markers. GABA has profound anxiolytic effects and dampens behavioral and physiological reactions to stressors, partially inhibiting the corticotrophin releasing hormone (CRH)-norepinephrine circuits participating in the mediation of fear and stress responses (Sherin, Nemeroff, 2011).

A study by Vaiva et al. (2004) showed a lower premorbid level of GABA in blood plasma of road-traffic victims with PTSD as compared to trauma-exposed participants that had not developed PTSD symptoms. This study also showed that the circulating level of GABA increased after recovery from PTSD. Furthermore, plasma GABA levels above 0.20 mmol/ml were not only protective, but also predicted recovery from PTSD (Vaiva et al., 2006). In contrast, Schur et al. (2016a) reported that PTSD symptoms were positively associated with GABA blood levels, although this association may be explained in part by their comorbid mental pathology. It is noteworthy that GABA levels in plasma and cerebrospinal fluid (Uhlhaas et al., 1986), correlate with GABA receptor binding in the anterior and posterior cingulate cortex, temporal cortex, and insula (Klumpers et al., 2010).

Progress in prevention and treatment of PTSD is hampered because studies indicate variability in the level of circulating cortisol, while data on thyroid hormone, testosterone and GABA are limited. The utility of biomarkers depends on many factors, such as the presence of concomitant comorbid pathology and the nature, duration and frequency of the traumatic experience. Moreover, in most studies, changes in blood concentration of cortisol are presented in cohorts of PTSD patients with trauma experienced no more than 6–8 years ago even though PTSD symptoms may persist for much longer periods of time. In our study, we, therefore, have extended the measurement of blood plasma concentration of cortisol with that of thyroid hormones, testosterone, and GABA in men with a trauma history of more than 10 years. Moreover, among trauma survivors, resistance to PTSD was studied by including a traumatized healthy cohort (Pitman et al., 2012).

2. Methods

2.1. Participants and procedure

The sample consisted of 108 men aged 30–45 years. Seventy-four men were veterans of the Chechen war (1996–2009) who had traumatic combat experiences. The period of participation in combat operations ranged from 3 months to 3 years. All veterans were recruited from the Chelyabinsk regional clinical therapeutic hospital for war veterans. The control group consisting of 34 healthy men with no history of traumatic experience and included 10 police officers with exclusively administrative duties. To estimate the number of participants needed in the study, a sample size calculation was performed using G Power Software version 3.1.9.2 (Düsseldorf, Germany) for ANOVA (one-way), using a rejection criterion of 0.05 and 0.95 (1- β) power, and large effect ($f = 0.4$). The power calculation indicated that a minimum of 34 participants (for each group) was required to be able to find such an effect (Faul et al., 2007).

PTSD symptoms were assessed by the Clinician-Administered PTSD Scale (CAPS), adapted to the Russian language sample (Tarabrina, 2001), 10 years after exposure to traumatic events. In the “PTSD” group, we included study participants who had symptoms of all PTSD criteria according to DSM VI-TR. The “resistant” group includes participants who have experienced combat trauma that meets the DSM IV criterion A1 and A2, but did not meet one or more other DSM IV-TR PTSD criteria. We did not use the total score on the CAPS as the main criterion for PTSD but in the “PTSD” group, the total score on the CAPS scale is significantly higher than in the “resistant” group. The “healthy” group (control) did not have a history of traumatic experience and did not meet criterion A1 and A2 for the diagnosis of PTSD DSM VI-TR. In this study, DSM VI-TR was used, since DSM V does not have a CAPS scale adapted for the Russian language sample.

Participants with a history of head injury and any psychiatric disorders other than PTSD were excluded from the analysis.

The study was approved by the ethics committee of the South Ural State University (protocol EK-N^o38–12) and conducted according to the Helsinki declaration of human rights. After the study protocol and the nature of the procedures were fully explained, all participants gave written informed consent to participate.

2.2. Plasma samples, GABA level, and hormonal level measurements

Blood samples were collected in heparin containing tubes (Guangzhou Improve Medical Instruments Co., Ltd, China) between 8.00 and 11.00 a.m. for all participants (108 men). Then samples were centrifuged for 15 min at 1000 \times g at 2–8 °C within 30 min of the collection after which they were stored at –80 °C.

GABA plasma levels were measured and hormones using ELISA kit for Gamma-Aminobutyric Acid (CLOUD-CLONE CORP. USA), thyroid-stimulating hormone (TSH), cortisol, testosterone, triiodothyronine (T3), tetraiodothyronine (T4) (Company Alcor Bio, Russia) according to the manufacturer's instruction. Sensitivity of the ELISA was 9, 39 pg/ml for GABA, 10 nmol/l for cortisol, 0.2 nmol/l for testosterone, 0.05 mkME/ml for TSH, 0,5 pmol/l for T3, 1,0 pmol/l for T4. Within- and between-assay coefficients of the ELISA for cortisol, testosterone, TSH, T3, T4 and GABA in human plasma are less 15%.

2.3. Statistical analysis

Statistical analysis was performed in RStudio version February 1, 5019 (RStudio Team Inc., 2019) with R version 3.6.2 (R Core Team, 2019). Preliminary statistical analyses included descriptive statistics and assessment of the normality of distributions. Data normality was assessed with the Shapiro-Wilk test.

For normally distributed data mean and standard deviation values were used; conversely, we used median and interquartile range (IQR) to

characterise non-normally distributed data.

Outliers were defined as more than three interquartile ranges from the hinges of a standard boxplot, and deleted censored.

Group differences in cortisol, TSH, T3, T4, and testosterone levels were explored using one-way ANOVAs (univariate analysis of variance), Tukey's HSD test was used for post-hoc group comparisons. Group differences in GABA levels were estimated using the Kruskal-Wallis test, Dunn test was used to compute post-hoc between-group differences. To compare CAPS sum scores between PTSD and resistant groups Welch Two Sample *t*-test was used.

All analyses were two-tailed with the significance level set at $p < 0.05$. For adjustment for multiple testing we used Tukey HSD test (FWER ≤ 0.05).

3. Results

3.1. Descriptive statistics

In this sample, there were only men ($n = 108$, 100%). There were no significant differences in the age of participants between the groups (Table 1). The mean values of CAPS sum scores were 27.7 (SD = 19.76) for PTSD group and 5.22 (SD = 4.76) for resistant group. Difference in CAPS sum scores was statistically significant between PTSD and resistant groups ($t(40) = 6.73$, $p = 4.4 \times 10^{-8}$).

Table 1 displays information on participant's age, mean values, and standard deviation of hormone and GABA levels in the blood across three groups (healthy, PTSD, resistant) as well as the results of one-way ANOVA.

Note: TSH – thyroid-stimulating hormone; SD – standard deviation; KW – Kruskal-Wallis test; IQR – interquartile range.

As can be seen from Table 1, PTSD, resistant and healthy groups differ significantly in the mean (median) concentrations of GABA, cortisol and testosterone. There are no significant differences in age and thyroid hormone levels.

3.2. Differences between GABA groups

As shown in Fig. 1, the median values of the GABA level in the peripheral blood differ between groups (Kruskal-Wallis chi-square = 7.57, $p = 0.023$, $df = 2$). Significant differences were detected between PTSD group and healthy controls ($z = 2.74$, $p = 0.018$), (Table 2).

Group-wise comparisons are depicted in Table 2.

3.3. Differences between hormone groups

Cortisol levels across investigated groups were found to be different ($F(2, 104) = 17.2$, $p = 4.12 \times 10^{-7}$) with resistant group having the highest levels of cortisol and group of healthy participants having the lowest ones (Fig. 2).

Tukey HSD test revealed statistically significant difference between healthy controls and PTSD group and between healthy controls and resistant group. Difference in the levels of cortisol in blood between PTSD and resistant groups was not significant (Table 2).

Table 1

Descriptive statistics and group differences by age, cortisol, thyroid-stimulating hormone, T3, T4, testosterone, and GABA levels.

Variable	Healthy (n = 34)		PTSD (n = 37)		Resistant (n = 37)		Statistics
	Mean	SD	Mean	SD	Mean	SD	F-value
Age	37.13	2.97	39.08	3.94	38.59	3.41	2.16
Cortisol (nmol/l)	365.84	86.22	474.63	140.67	510.39	105.17	17.2
T3 (pmol/l)	6.05	1.18	5.63	1.49	6.1	1.24	1.15
T4 (pmol/l)	10.92	2.08	11.49	1.98	11.93	1.8	1.92
TSH (μIU/ml)	1.58	0.68	1.84	0.8	1.87	0.79	1.3
Testosterone (nmol/l)	15.58	5.89	16.9	7.12	19.84	5.81	4.47
	Median	IQR	Median	IQR	Median	IQR	KW chi-square
GABA (pg/ml)	76.03	57.21	56.59	15.82	66.82	25.46	7.57

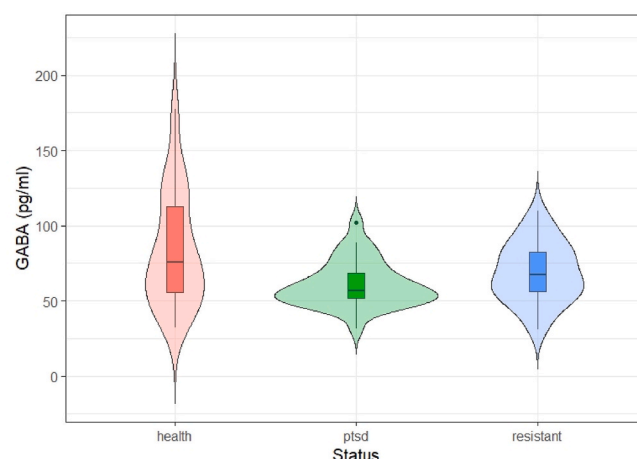


Fig. 1. Differences in median values of GABA levels across groups displayed as violin plots. The shape of these plots represents the distribution of sample values (mirrored along the middle line) with standard box-and-whisker plots inserted inside.

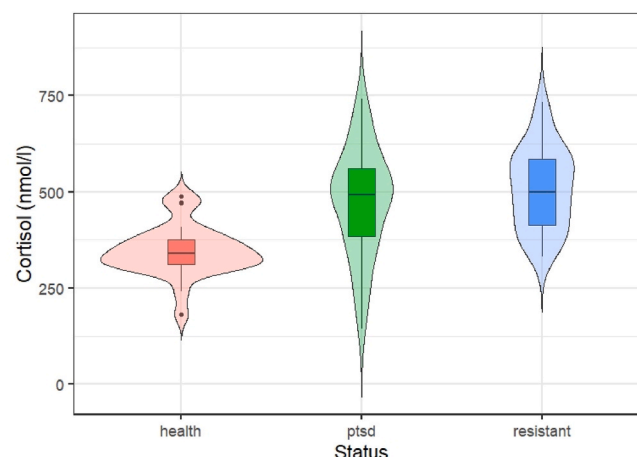


Fig. 2. Differences in mean values of cortisol levels across groups.

Results of one-way ANOVA showed that testosterone levels in the blood of participants differ between groups ($F(2,86) = 4.47$, $p = 0.0143$) (Fig. 3). As displayed in Table 2, the only difference between groups that passed statistical significance threshold of 0.05 was “healthy controls - resistant group” pair.

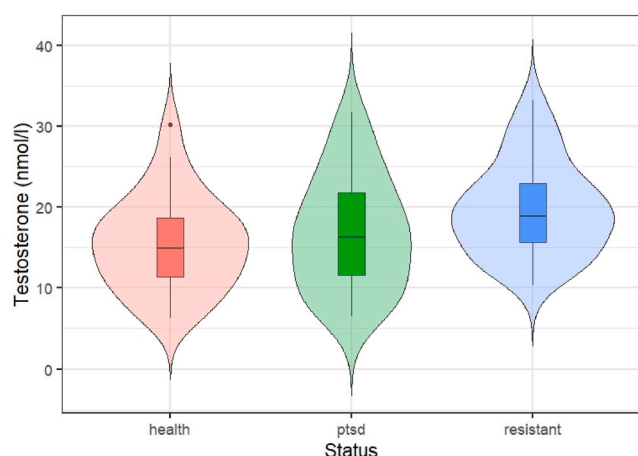
Mean levels of T3 (triiodothyronine), T4 (thyroxine) and TSH (thyroid-stimulating hormone) did not differ between groups ($F(2, 85) = 1.15$, $p = 0.321$; $F(2, 85) = 1.92$, $p = 0.153$; $F(2, 85) = 1.3$, $p = 0.277$, respectively).

Additionally, we directly compared GABA, cortisol, and testosterone blood levels in trauma-exposed (PTSD plus resistant groups) and

Table 2

Pairwise post-hoc comparisons between groups for GABA, cortisol and testosterone.

	Pair	Difference	Adjusted p-value	Effect size (Cohen's d)
GABA	PTSD-healthy	2.74	0.018	0.488
	Resistant – healthy	1.1	0.269	
	Resistant – PTSD	–1.67	0.189	
Cortisol	PTSD-healthy	108.79	5.67e-04	0.932
	Resistant – healthy	144.55	4.1e-06	
	Resistant – PTSD	35.76	0.391	
Testosterone	PTSD-healthy	1.33	0.7	0.728
	Resistant – healthy	4.26	0.03	
	Resistant – PTSD	2.94	0.175	

**Fig. 3.** Differences in mean values of testosterone levels across groups.

trauma-unexposed individuals. The results of statistical analysis showed that all differences between compared groups were statistically significant ($p < 0.05$). GABA level was higher in the healthy controls group ($t(43) = 2.31$, $p = 0.025$). Cortisol and testosterone levels were higher in the trauma-exposed group in comparison to trauma-unexposed participants ($t(67.58) = -3.94$, $p = 0.0002$; $t(62.4) = -2.53$, $p = 0.014$, respectively) (Fig. 4). As matter of sensitivity analysis we compared hormone levels between not trauma exposed police officers in the control group and controls with other professions and found no significant differences.

4. Discussion

4.1. Cortisol, testosterone, and thyroid hormones

This study reports a significantly higher level of cortisol in the military suffering from PTSD group ($N = 37$) and a PTSD resistant group ($N = 37$), compared to an untraumatized a control group ($N = 34$). This finding disagrees with the common notion that am cortisol levels of PTSD patients are usually lower than controls, particularly if the 'cortisol awakening response' is measured. Such a reduced circulating cortisol level in PTSD patients has been explained as a sign of enhanced glucocorticoid feedback (Yehuda et al., 1993) (Rauch et al., 2020). However, the finding does not exclude that PTSD patients actually may be more susceptible to stressors which may produce an overall higher circulating cortisol level as was suggested by Steudte et al. (2011).

In line with the above suggestion it is therefore possible that an increase in cortisol levels in the "PTSD" and "PTSD-resistant" groups compared to the "healthy" group can be explained by the history of traumatic experience, regardless of the presence or absence of PTSD. In support, Golier et al. (2012), (2014) reported a higher reactivity of the adrenal cortex in response to stimulation with either corticotropin releasing factor (CRF) or corticotropin in veterans exposed to the military operation itself irrespective PTSD or not, than in veterans who did not serve in combat. A study by De Kloet et al. (2007) showed increased cortisol suppression in response to dexamethasone in war-stressed individuals, also regardless of whether or not they had PTSD, as compared to healthy controls.

These studies agree that in veterans a history of trauma, regardless of PTSD history, the susceptibility to both stimulatory as well as inhibitory effects in HPA axis regulation was increased. This suggests that as a result of increased stress responsivity and enhanced feedback action, the reactivity of the HPA axis is enhanced (Golier et al., 2014). Depending on the circumstances hyper- or hypocortisolemia is found. These examples illustrate the intricate relationship between traumatic experience, PTSD-susceptibility or resistance and cortisol levels. Notwithstanding the many papers devoted to this topic, the contribution of potential confounders including sex (Zorn et al., 2017), has yet to be addressed in future studies.

Significant differences in testosterone level were present between resistance groups and healthy respondents ($p < 0.01$), while neither the PTSD vs resistance groups nor the PTSD vs healthy respondents differed significantly. The absence of significant differences in testosterone level between the PTSD groups and the healthy control group is consistent with the studies of Spivak et al. (2003) and Lehrner et al. (2016). Our results are also consistent with the study by Reijnen et al. (2015) showing no difference in testosterone level between PTSD and PTSD-resistant patients. It is possible that increased testosterone levels in the resistant group contribute to PTSD resistance (Josephs, 2017), but this question obviously requires further research.

In our study, no significant differences were present between the studied groups in the levels of the thyroid hormones and thyroid stimulating hormone, which casts doubt on their significance as a biomarker at least in this group of military. Yet, it cannot be ruled out that thyroid hormone is informative in other PTSD cohorts, and this issue also need further research.

4.2. GABA

The GABA plasma levels of the PTSD groups was significantly lower that their healthy controls ($p < 0.05$), a finding that is consistent with previous studies studying a sample of individuals with PTSD symptoms 6 weeks and 1 year after the traumatic experience, respectively (Vaiva et al., 2004, 2006). These data support previous findings showing that GABA levels were decreased in cortical and subcortical brain structures using magnetic resonance spectroscopy (MRS), as well as in blood plasma (Rosso et al., 2013; Ghosal et al., 2017; Sheth et al., 2019). Accordingly, the decrease in GABA blood level observed in our PTSD patients with a more than ten years history of trauma, possibly may reflect a decrease in central GABA-ergic activity and consequent altered processing of fear and anxiety (Lydiard 2003).

However, Schur et al. (2016b) reported a significant increase in blood GABA levels in military personnel suffering from PTSD at 6 months after military service, but these patients had additional mental problems and depressive symptoms. The increase rather than a decrease is explained by the authors as a compensatory mechanism in response to the accumulation of psychopathologies.

5. Limitations

A limitation of our study is that a single timepoint between 8.00 and 10.00 AM rather than patterns of cortisol secretion were measured, even

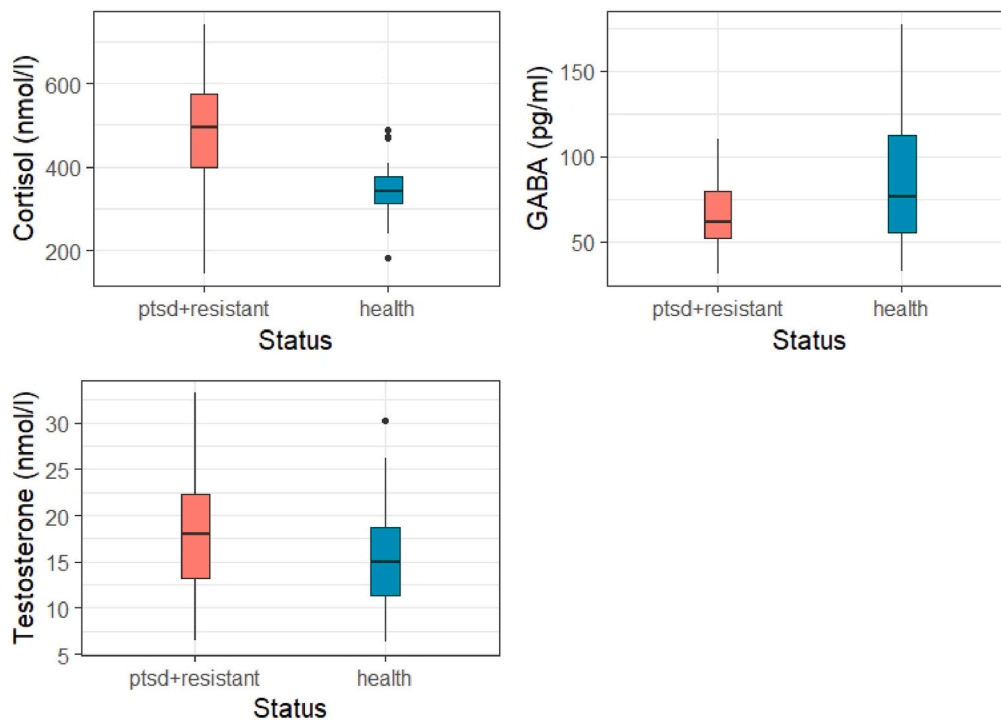


Fig. 4. Differences in blood levels of GABA, cortisol, and testosterone in individuals who have been exposed to trauma and those who have not been exposed to trauma.

though we present data of $n = 34\text{--}37$ individuals in PTSD and control groups. Such patterns may include for instance the rise in cortisol upon awakening (Rauch et al., 2020) or the cortisol ultradian rhythm (Walker et al., 2012). However, there is no reason to assume this variation was not equally distributed between the diagnostic groups, although bias cannot be ruled out. Another limitation is the control group of (“healthy”) police officers whose professional activities may be associated with a different everyday stressor exposure than occurring in the general population.

6. Conclusion

In this study we found that in males the circulating cortisol, testosterone and GABA levels differed from the control values even at 10 years after a traumatic experience that precipitated PTSD. Of particular interest is that the higher levels of cortisol did not depend on the presence or absence of PTSD. Testosterone levels were higher in the traumatized, but not PTSD group, than in controls. This finding suggests that the stress- and sex hormones may have potential as biomarker of the long-term consequences of the traumatic experience per se. In contrast, GABA can be considered a marker of the protracted nature of PTSD.

Author contributions

Inna Feklicheva – Conceptualization, Methodology, Writing - Original Draft; **Marco P. Boks** – Conceptualization, Writing - Review & Editing; **E. Ron de Kloet** - Writing - Review & Editing; Supervision; **Nadezda Chipeeva** - Data curation, Investigation, Writing - original draft; **Ekaterina Maslennikova** - Data curation, Investigation; **Anton Pashkov** - Formal analysis, Visualization; **Svetlana Korobova** - Writing - original draft; **Mariia Komelkova** – Investigation; **Yulia Kuznetsova** - Investigation; **Pavel Platkovski** - Investigation; **Marina Mamonova** - Resources, acquisition of data **Olga Sidorenko** - Resources, acquisition of data **Tatyana Vasilenko** - Resources, acquisition of data **Olga – Tseilikman** - Resources, acquisition of data **Vadim Tseilikman** - Conceptualization, Methodology, Writing - Original Draft.

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Declaration of competing interest

None.

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