

## Clinical Psychopharmacology and Neuroscience - Manuscript

### Submission

- **Manuscript ID:** CPN-21-846
- **Title:** Association between dissociative symptoms and morning cortisol levels in patients with post-traumatic stress disorder
- **Running Title:** Dissociative subtype and cortisol levels in PTSD group
- **Article Type:** Original Article
- **KeyWords:** post-traumatic stress disorder, dissociative subtype, morning serum cortisol level, hypocortisolism, Hypothalamic-pituitary-adrenal axis, childhood trauma

## ABSTRACT

**Objectives:** Patients with post-traumatic stress disorder (PTSD) showed inconsistencies in their cortisol level, an index of the hypothalamic-pituitary-adrenal (HPA) axis function. This study examined the relationship between dissociation, childhood trauma, and morning cortisol levels in PTSD patients.

**Methods:** This study included 69 (23 males and 46 females) patients and 82 (22 males and 60 females) healthy controls (HCs). Clinical assessments, including the Childhood Trauma Questionnaire (CTQ) and Peri-traumatic Dissociative Experiences Questionnaire scores (PDEQ), and morning cortisol levels were evaluated. The morning cortisol levels were compared between PTSD with high dissociation (PTSD-HD) and low dissociation (PTSD-LD) groups. The effect of CTQ subtype on morning cortisol levels was analyzed.

**Results:** The PTSD with high dissociation group showed significantly lower cortisol levels than that of the PTSD-LD and HC groups. A significant inverse correlation was found between cortisol levels and dissociation. A significant positive correlation was found between dissociation and physical abuse and sexual abuse scores. Morning cortisol levels showed a significant positive correlation with emotional abuse, emotional neglect, and physical neglect, respectively. There was no moderating or mediating effect of CTQ on the relationship between cortisol level and dissociation.

**Conclusions:** These findings suggest that dissociation is a significant factor related to hypocortisolism in PTSD patients. Additionally, basal morning cortisol levels and dissociation scores were closely associated with childhood trauma.

**Keywords:** post-traumatic stress disorder; dissociative subtype; morning serum cortisol level; hypocortisolism; Hypothalamic-pituitary-adrenal axis; childhood trauma

## INTRODUCTION

Hypothalamic-pituitary-adrenal (HPA) dysregulation is an essential stress response factor in understanding the pathophysiology of post-traumatic stress disorder (PTSD) [1]. Cortisol, one of the primary hormones reflecting fluctuations in the HPA axis, enables the stress response and inhibits the ongoing HPA axis activity through negative feedback mechanisms. A much discussed question is whether cortisol could be used as a sensitive marker for PTSD patients. Although a large body neuroendocrine studies have noted cortisol alterations in PTSD patients, some incongruence exists across the findings. Studies of basal morning blood cortisol levels and PTSD severity have reported conflicting results: some studies found no definite relationship [2] whereas others detected blunted cortisol levels in PTSD groups when compared to healthy controls [3].

These inconsistencies can be attributed not only to the methodological differences [4] but also heterogeneity within the PTSD group, including comorbid disorders [5], chronicity, types, and duration of the illness [2]. Further, emerging research has identified the divergent impact of the dissociative subtype of PTSD on cortisol levels [6-8]. The patients of this distinct PTSD subgroup exhibit an emotional detachment following traumatic events in the form of depersonalization or derealization [9]. Several studies have reported that patients with higher dissociation levels showed reduced blood cortisol levels when compared to those with lower dissociation levels [6, 8].

Childhood trauma experiences have been identified as strong risk factors for adult PTSD development [10]. Furthermore, childhood adversity is strongly associated with hypocortisolism [11] and the dissociative subtype of PTSD [12, 13]. A history of childhood trauma is a probable point of intersection of hypocortisolism and dissociative symptoms. Although empirical studies have established strong associations between childhood trauma and the development of

dissociative symptoms, only a few studies have accounted its potential impact on cortisol levels in PTSD patients [14].

This study aimed to investigate the relationship between dissociative symptoms and the morning serum cortisol levels in PTSD patients and healthy controls. We hypothesize that the dissociation severity is significantly correlated with the morning cortisol levels in the PTSD group. We examined the association between childhood traumatic experience and cortisol levels as well as that between childhood traumatic experience and dissociation levels. Furthermore, we analyzed the possible moderating or mediating effect of childhood traumatic experience on the relationship between cortisol levels and dissociation.

## **METHODS**

### **Participants**

This study recruited 69 patients with PTSD (23 males and 46 females) and 82 healthy controls (HCs; 22 males and 60 females) from the Psychiatry Department. The diagnosis of PTSD was based on DSM-5 [9] and the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) by a psychiatrist. **Peri-traumatic Dissociative Experience Questionnaire (PDEQ) was assessed to measure the dissociation level of participants with PTSD. Given the ease of analysis and interpretation [15], we performed a median split ( $> 16$  vs.  $\leq 16$ ) to transform the PDEQ score into two discrete groups: patients with high dissociation level (PTSD-HD) and with low dissociation level (PTSD-LD).** The HCs were recruited from the local community through fliers and posters, and they were examined by a psychiatrist. The HCs had no history of mental disorders or major physical trauma (i.e., a severe car accident, combat experience, sexual assault, serious physical

injury including traumatic brain injury, etc.), and were not taking medications with probable psychoactive effects at the time. As for the PTSD group, we excluded participants with a history of or current diagnosis of any psychiatric, substance abuse and/or neurological disorder other than PTSD, such as schizophrenia, bipolar disorder, anorexia nervosa, alcohol dependence, epilepsy and etc. 15 patients were identified as drug-naive patients at the time of recruitment. A total of 25 different types of medications were prescribed across PTSD patients, which were Aripiprazole (n = 1, 2mg), Blonanserin (n = 4, 4mg), Olanzapine (n = 6, 2.5 - 5mg), Quetiapine (n = 15, 25 - 300 mg), Valproate (n = 3, 300 - 500 mg), Duloxetine (n = 1, 60mg), Escitalopram (n = 19, 5 - 20mg), Vortioxetine (n = 11, 5 - 20mg), Paroxetine (n = 2, 12.5mg), Desvenlafaxine (n = 5, 50 - 100 mg), Fluoxetine (n = 1, 20mg), Sertraline (n = 3, 50 - 100mg), Venlafaxine (n = 3, 75mg), Etizolam (n = 8, 0.25 - 0.5 mg), Alprazolam (n = 13, 0.25 - 0.5 mg), Lorazepam (n = 10, 0.5 - 1m), Busprione (n = 9, 5 - 15 mg), Clonazepam (n = 21, 0.5 mg). Further, many (n = 63) were prescribed with more than one medication (e.g., Sertraline, Alprazolam, and Clonazepam). Participants were excluded from the study if they reported any traumatic brain injury. All participants signed an informed consent form approved by the Institutional Review Board before participating (IRB no. 2015-07-025).

## **Psychological Measures**

### Post-traumatic Stress Disorder checklist

To examine the severity of the PTSD symptoms, the Korean version of the Post-traumatic Stress Disorder Checklist (PCL) was administered [16]. This instrument is a self-reporting rating scale for assessing DSM-IV symptoms of PTSD. It consists of 17 items that are assessed using a five-

point Likert scale ranging from one (“not at all”) to five (“extremely”).

#### Peri-traumatic Dissociative Experiences Questionnaire

This study used the Korean validated version of the PDEQ [17]. This eight-item instrument, rated on a scale ranging from one (“not at all true”) to five (“extremely true”), asks respondents to what extent they experienced depersonalization, derealization, and altered sensations at the time of the traumatic events (e.g., “What was happening did not seem real, like I was in a dream or watching a movie”). The PDEQ has demonstrated satisfactory internal consistency (0.75), test-retest reliability (0.85), and high equivalence to the original PDEQ with evidence of discriminant, and the convergent construct validity was significant. This instrument has shown a good level of reliability and validity in Korean samples.

#### Hospital Anxiety and Depression Scale

The Korean-validated version of the Hospital Anxiety and Depression Scale (HADS) was used to assess symptoms of anxiety and depression [18]. It consists of seven items each for anxiety and depression, with a four-point Likert scale ranging from zero (“no problems”) to three (“maximum distress”). This version has proven its extensive validation and reliability in Korean samples.

#### Childhood Trauma Questionnaire

The Korean validated version of the Childhood Trauma Questionnaire (CTQ) [19] consists of five subscales of various childhood traumas, such as emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect, and another scale for detecting minimization and denial.

(The CTQ consists of 28 items and is assessed using a five-point Likert scale ranging from one (“never true”) to five (“very often true”). The Korean-validated version of the CTQ is known to have reliability and validity.

### **Blood sample analysis**

Blood sampling was conducted between 6:00 AM and 10:00 AM prior to breakfast consumption. Blood samples were centrifuged at 3017 revolutions/minute for 10 minutes at 10°C. Serum cortisol was analyzed by the Laboratory Medicine Department using an electrochemiluminescence immunoassay (ECLIA, Cobas 8000 Roche Diagnostics, Korea) with a coefficient of variation of 3.8% (measurement range 0.054-63.4 µg/dL) [20].

### **Statistical analysis**

For normality test, the skewness over 2.0 and kurtosis over 7.0 were considered non-normal. All variables in our results were within the range of normal distribution. The sociodemographic and clinical assessment variables were compared across groups using  $\chi^2$ - and F-tests. A One-way ANOVA was used to determine any difference among the three groups (PTSD-HD, PTSD-LD, and HC) in basal morning cortisol levels. Covariates including body mass index [21], duration of illness, education, anxiety, depression, PTSD symptom severity, number of PTSD symptoms, alcohol consumption [22], and cigarette smoking [23] were controlled. As a post-hoc analysis, pairwise comparisons with the Bonferroni method using the least significant difference were performed. A power analysis using the G\*Power 3.1 program [24] was conducted to estimate power ( $1 - \beta$ ) set at  $\alpha = 0.05$  based on the effect size parameter, and the adequate sample size used

in a study. For the analysis of Pearson correlation, the residualized value with age, sex, BMI, HADS-Anxiety, and HADS-Depression as covariates was applied. We calculated the residualized values by executing a linear regression with the outcome variable as the dependent variable and only the covariates (i.e., age, sex, body mass index, HADS-Anxiety, and HADS-Depression) as the independent variables. The residualized values of cortisol, dissociation, and the five CTQ subtypes (i.e., sexual abuse, emotional abuse, physical abuse, emotional neglect, and physical neglect) were obtained. A 5000-bootstrap resampling technique was applied to correct for multiple correlations. Further, we examined the potential moderation or mediation effect of the CTQ score and its five subtypes on the relationship between cortisol and dissociation. We also tested whether dissociation had any moderating and mediating effect on the relationship between cortisol and CTQ variables. The analysis of moderation and mediation was conducted using the Johnson-Neyman technique [25] installed in Statistical Package for the Social Sciences (SPSS) as macro PROCESS version 3.5. All significant levels were set at  $p < 0.05$ , and all statistical analyses were carried out using SPSS software (version 21.0; IBM Corp., Armonk, NY, USA).

## **RESULTS**

### **Descriptive Statistics**

Table 1 shows the demographic and psychological characteristics among PTSD with high dissociation group, PTSD with low dissociation group, and HCs. The education was significantly different among the three groups; HCs showed a significantly higher education than PTSD with high dissociation and low dissociation ( $12.27 \pm 2.43$  vs.  $12.28 \pm 3.34$  vs.  $13.91 \pm 3.38$ ,  $p = 0.008$ ). The PDEQ and the DES-II were significantly higher in PTSD with high dissociation than PTSD

with low dissociation and HCs (PDEQ:  $24.85 \pm 4.96$  vs.  $11.58 \pm 2.48$  vs.  $8.70 \pm 1.15$ ,  $p < 0.001$ ; DES-II:  $36.70 \pm 21.10$  vs.  $7.29 \pm 7.38$  vs.  $2.55 \pm 3.74$ ,  $p < 0.001$ , respectively). The PCL-5 scores were significantly lower in HCs than in PTSD with high dissociation and low dissociation (PCL-5:  $56.61 \pm 9.10$  vs.  $40.06 \pm 1.90$  vs.  $11.35 \pm 9.82$ ,  $p < 0.001$ ). The CAPS and HADS score were significantly lower in HCs than in PTSD with high dissociation and low dissociation (CAPS-severity:  $42.81 \pm 8.26$  vs.  $37.14 \pm 11.95$  vs.  $6.16 \pm 7.68$ ,  $p < 0.001$ ; CAPS-number of symptoms:  $14.31 \pm 2.13$  vs.  $11.92 \pm 3.17$  vs.  $2.05 \pm 2.86$ ,  $p < 0.001$ ; HAD-anxiety:  $15.58 \pm 3.32$  vs.  $10.28 \pm 3.56$  vs.  $4.54 \pm 2.26$ ,  $p < 0.001$ ; HAD-depression:  $14.39 \pm 3.44$  vs.  $10.50 \pm 3.3$  vs.  $4.83 \pm 2.41$ ,  $p < 0.001$ ).

### **Basal cortisol levels**

We found a significant difference in basal cortisol among three groups (Fig. 1;  $4.83 \pm 1.64$  vs.  $10.70 \pm 1.083$ , vs.  $13.11 \pm 1.01$  ug/dL;  $F = 8.816$ ,  $df = 2$ ,  $p < 0.001$ ). Post hoc analysis revealed that PTSD group with high dissociation showed significantly lower basal cortisol than PTSD group with low dissociation ( $p < 0.001$ ) and HCs ( $p = 0.001$ ). The effect size was small ( $d = 0.2564$ ) and the power was 0.80.

### **Correlation between Childhood Trauma Questionnaire subtypes, dissociation, and basal cortisol levels**

Among patients with PTSD ( $n = 69$ ), basal cortisol level significantly correlated with dissociation ( $r = -0.265$ ,  $p = 0.028$ ), Emotional Abuse (EA) ( $r = 0.341$ ,  $p = 0.004$ ), Physical Neglect (PN) ( $r = 0.285$ ,  $p = 0.018$ ) and Emotional Neglect (EN) ( $r = 0.314$ ,  $p = 0.009$ ). Dissociation significantly

correlated with Physical Abuse (PA) ( $r = 0.355$   $p = 0.003$ ) and Sexual Abuse (SA) ( $r = 0.270$ ,  $p = 0.020$ ). Fig. 2 shows correlation scatter plots created based on residualized values of dissociation, basal cortisol, and subtypes of CTQ in patients with PTSD.

### **Mediation and moderation analysis among Childhood Trauma Questionnaire subtypes, dissociation, and basal cortisol levels**

The moderation model used to predict cortisol levels from CTQ and dissociation did not show significant results ( $p = 0.1545$ ). The two mediation models between dissociation and cortisol with CTQ as a mediator ( $p = 0.1386$ ), and between CTQ and cortisol with dissociation as a mediator ( $p = 0.138$ ) did not show significant results.

## DISCUSSION

In this study, we evaluated the relationship between morning cortisol levels, dissociation severity, and childhood trauma in PTSD patients when compared to HCs. The PTSD-HD group showed significantly lower morning cortisol levels as compared to the PTSD-LD and HC groups. Among patients with PTSD, there was a significant negative correlation between dissociation and morning serum cortisol levels. Furthermore, dissociation showed a significant positive correlation with emotional abuse and sexual abuse. Morning serum cortisol levels had a strong positive correlation with emotional abuse, physical neglect, and emotional neglect. These correlations remained salient even after controlling for covariates of age, sex, BMI, severity of anxiety, and severity of depression.

The main findings of the study were that PTSD-HD patients showed the lowest morning serum cortisol levels. Hypocortisolism among PTSD groups has been observed in majority of previous findings [3]. Our study highlights the importance of dissociative symptoms in the regulation of cortisol levels in patients with PTSD. This finding supports enhanced negative feedback in the dissociative subtype of PTSD [26]. Previous reports have shown that non-dissociative PTSD exhibits trauma-related undermodulation characterized by hyperarousal symptoms, whereas dissociative PTSD displays emotional overmodulation characterized by depersonalization or derealization [7]. The pronounced hypocortisolism in the dissociative subtype could be explained by a significant negative correlation between disengagement coping strategy and cortisol levels [27]. The lower cortisol levels or corticolimbic inhibition of PTSD patients with high dissociative symptoms provides evidence regarding the emotional overmodulation model of the dissociative subtype that distinguishes it from non-dissociative PTSD.

There was a significant negative correlation between dissociation severity and morning serum cortisol levels in PTSD patients. Depression and anxiety often concur with PTSD symptoms [28, 29] and their hypercortisolism potential interfere with cortisol secretion. Although no patients in our PTSD sample reported a history of any depressive disorders or anxiety disorders, we accounted for their possible confounding effect on the cortisol levels. Thus, our results clearly demonstrate that PTSD patients with dissociative symptoms bereft of comorbid anxiety and depression symptoms tend to have lower levels of morning serum cortisol.

Within the PTSD group, a significant positive correlation was found between dissociation and the physical abuse and sexual abuse scores. Higher levels of dissociation in adulthood have been related to childhood maltreatment in both PTSD patients and general population [12, 30]. In particular, physical abuse and sexual abuse, but not neglect, have been associated with dissociation [30, 31]. This implies that exposure to physical and sexual abuse in childhood is more closely related to the development of dissociative symptoms. Children who have experienced physical abuse or sexual abuse tend to display deficits in emotional regulation and expression [27]. Early exposure to sexual or physical abuse could primarily lead to the development of a dissociative coping strategy to disconnect from the actual psychologically distressing situations [31]. Thus, sexual or physical abuse in childhood may be strongly associated with adult dissociative symptoms in PTSD patients.

Additionally, morning serum cortisol levels showed a significant positive correlation with emotional abuse, emotional neglect, and physical neglect. Previous studies have reported strong association between physical and sexual childhood trauma and cortisol levels [10, 32, 33]. Individuals with a history of emotional neglect, physical neglect [34] or emotional abuse [35] tend

to show elevated basal cortisol levels. This may reflect a divergent relationship between different childhood trauma subtypes and HPA-axis functioning.

Our study had some limitations. First, we did not control the dosage, **types**, and duration of medications. **Given the possible effects of medication on morning cortisol levels [36, 37] future research should adjust the related factors.** Second, PTSD patients recruited in this study were not strictly homogeneous in terms of their trauma types (e.g., the patient group included victims of traffic accidents, defectors, etc.). Lastly, this was a cross-sectional study and the assessment of the cortisol was limited to one time per subject. **This measure was then correlated with psychological assessments from self-report questionnaires.** Although we included the duration of illness in the main analysis, further serial follow-up studies are needed.

Our results suggest that the morning serum cortisol levels were significantly lower in the PTSD-HD group and negatively correlated with dissociation level within the PTSD group. Additionally, childhood traumatic experience and dissociation showed statistically significant positive correlations. Our findings support the hypothesis that HPA axis dysregulation reflected by hypocortisolism is markedly present in PTSD-HD patients. Thus, different types of childhood traumatic experiences discretely relate to cortisol levels or to dissociative symptoms. Clinicians may consider the presence and influence of dissociative symptoms and childhood traumatic experiences within patients with PTSD when assessing their stress regulatory dynamics. Further biological studies are warranted to understand the underpinning interplay among dissociative subtype, childhood traumatic experiences, and morning serum cortisol in PTSD patients.

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**Conflicts of Interest**

The authors have no potential conflicts of interest to declare.

**Author contributions**

H.S.L was responsible for the critical writing and editing of the manuscript. H.S.L and D.I.M conducted all major statistical analyses and drafting of the manuscript. S.H.L and H.S.L were responsible for the conceptualization, design, and editing of the study. S.H.L supervised the study protocol, data acquisition, analysis, and editing. S.Y.B, A.K, and M.J.J were responsible for data collection and minor statistical analysis. All authors have read and agreed to the published version of the manuscript.

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Table 1.  
Demographic and clinical characteristics of participants

	PTSD-HD <sup>a</sup> (N = 33)	PTSD-LD <sup>b</sup> (N = 36)	HC <sup>c</sup> (N = 82)	$\chi^2/F$	<i>p</i> -value	Post-hoc (Least Significant Difference)
Age (years)	45.33 (12.22)	45.22 (13.07)	47.15 (13.13)	.393	0.675	
Sex (male/female)	13/20	10/26	22/60	1.868	0.393	
Education (years)	12.27 (2.43)	12.28 (3.34)	13.91 (3.38)	4.947	0.008	a < c, b < c
PDEQ	24.85 (4.96)	11.58 (2.48)	8.70 (1.15)	414.762	< 0.001	b > c, a > b, c
PCL - 5	56.61 (9.10)	40.06 (1.90)	11.35 (9.82)	263.969	< 0.001	b > c, a > b, c
CAPS - Severity	42.81 (8.26)	37.14 (11.95)	6.16 (7.68)	263.573	< 0.001	b > c, a > b, c
CAPS - Number of symptoms	14.31 (2.13)	11.92 (3.17)	2.05 (2.86)	292.072	< 0.001	b > c, a > b, c
HADS-Anxiety	15.58 (3.32)	10.28 (3.56)	4.54 (2.26)	186.831	< 0.001	b > c, a > b, c
HADS-Depression	14.39 (3.44)	10.50 (3.33)	4.83 (2.41)	143.109	< 0.001	b > c, a > b, c

Note: Categorical variables are represented as percentages and means (standard deviations) are represented as continuous variables.

PTSD-HD = Post-traumatic stress disorder with High Dissociative subtype. PTSD-LD = Post-traumatic stress disorder with Low Dissociative subtype. HC = Healthy control. PDEQ = Peri-traumatic Dissociative Experiences Questionnaire. PCL-5 = PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders (DSM-5). CAPS = Clinician Administered PTSD Scale for DSM-5. HADS = Hospital Anxiety and Depression Scale.



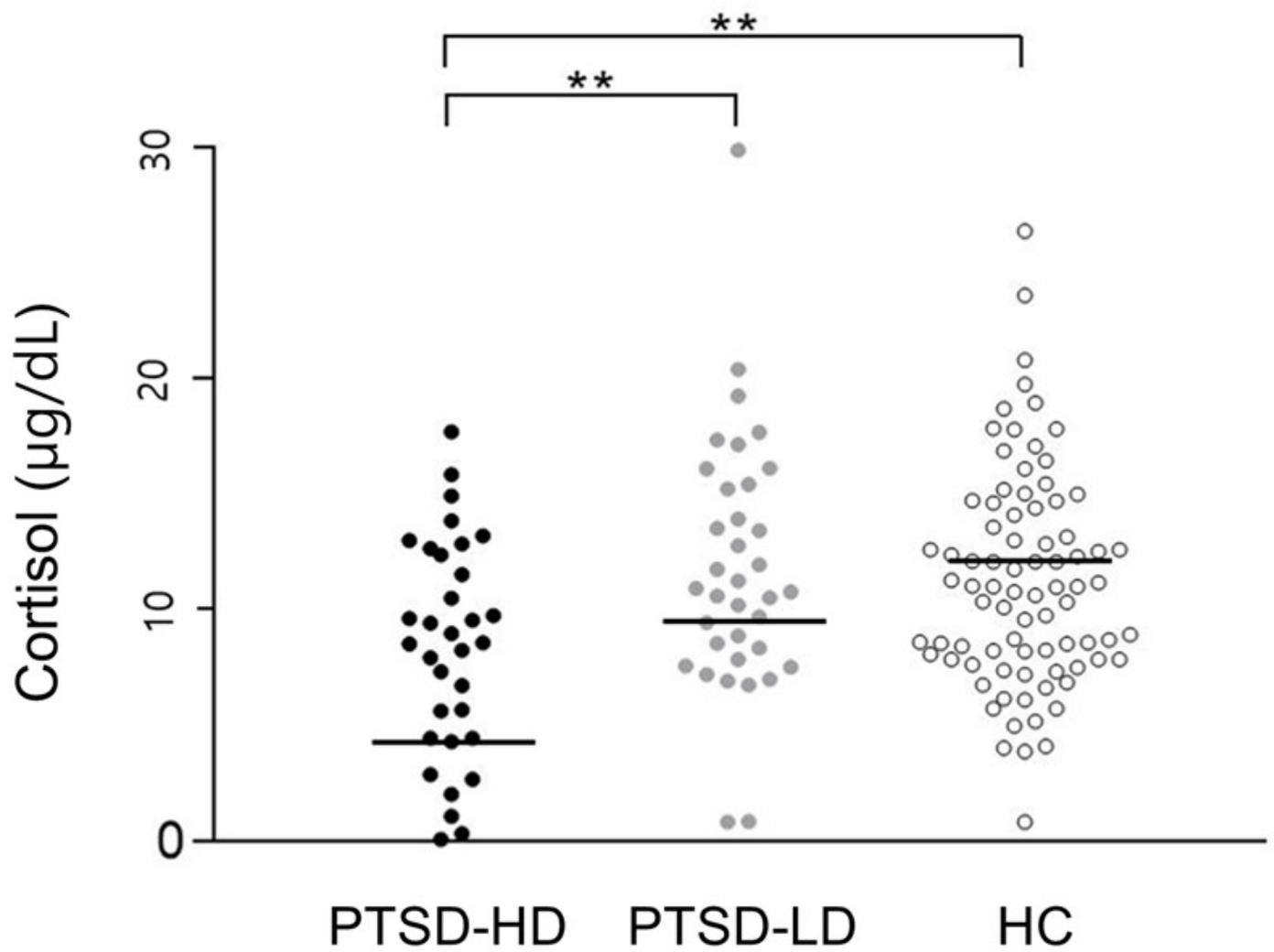


Fig. 1. Basal serum cortisol level in PTSD group with High Dissociation (PTSD-HD), PTSD group with Low Dissociation (PTSD-LD), and the Healthy Control (HC) group. Horizontal bars represent mean values. \*\*  $p < 0.01$

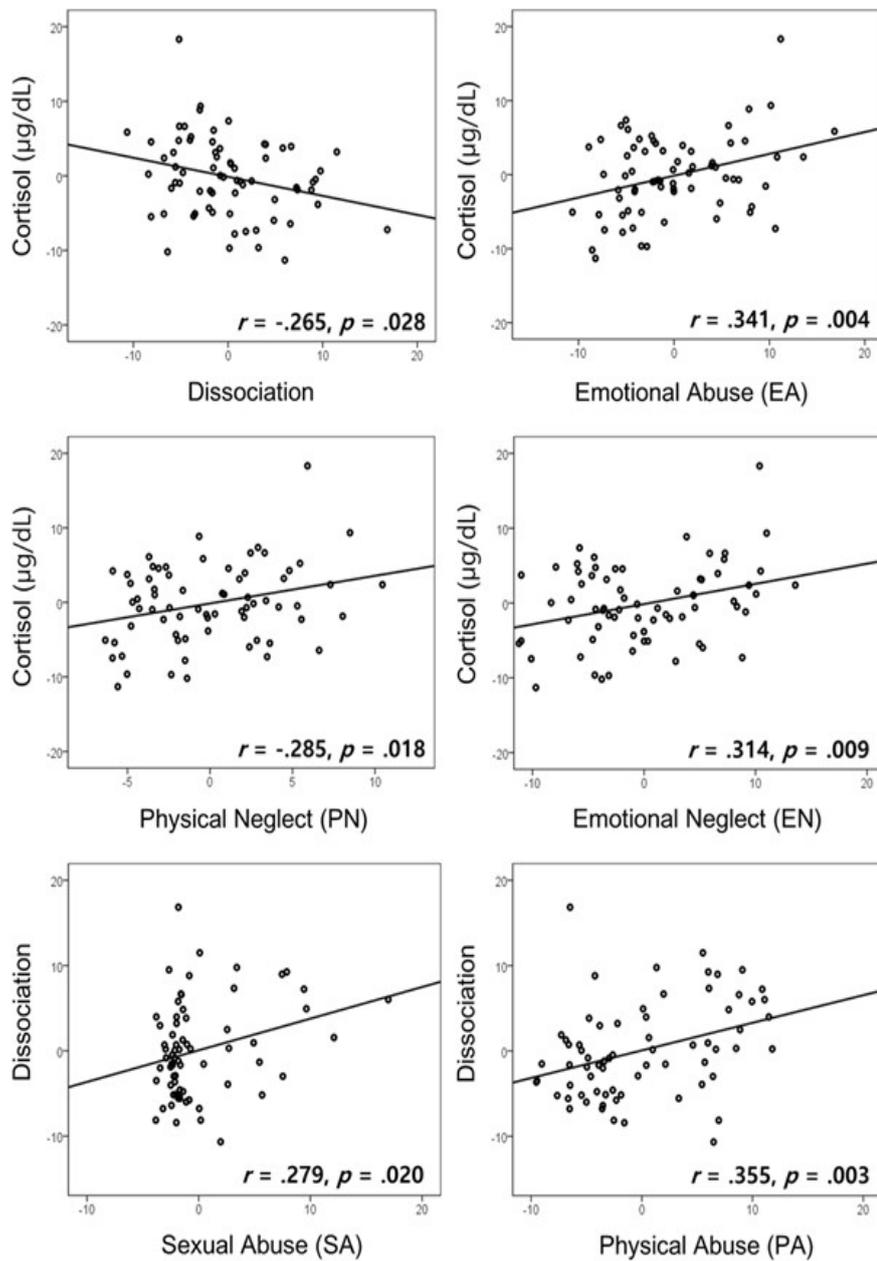


Fig. 2. Correlations between childhood trauma questionnaire (CTQ) subscales, basal serum cortisol level and Peri-traumatic Dissociative Experiences Questionnaire (PDEQ) in patients with PTSD (n = 69). Age, sex, BMI, HADS-Anxiety, and HAD-Depression were included as covariates.