

Research paper

Mineralocorticoid receptor stimulation effects on stress-induced cortisol and alpha-amylase in female patients with borderline personality disorder and healthy controls: A randomized placebo-controlled experimental study

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ABSTRACT

Borderline personality disorder (BPD) has been associated with alterations in the hypothalamic-pituitary-adrenal (HPA) axis, such as a blunted cortisol response to acute psychosocial stress. The mineralocorticoid receptor (MR) is involved in HPA-axis feedback regulation and plays a key role in stress regulation. In response to stress, pharmacological blockade of the MR leads to exaggerated cortisol release, but MR stimulation has not been investigated in BPD. This is of special interest as altered hippocampal feedback regulation, possibly due to MR dysfunction, has been suggested in BPD. In a double-blind, randomized design, 120 female patients with BPD and 120 healthy controls (HC) received 0.4 mg fludrocortisone or placebo. Two hours later, participants were exposed to the Trier Social Stress Test (TSST) or a placebo version (pTSST). Salivary cortisol and alpha-amylase (sAA) were collected at baseline (T0), +120 min (T1, pre-(p)TSST), +135 min (T2) and + 195 min (T3) after drug intake. Despite reporting higher subjective affective response to stress, patients with BPD exhibited a blunted cortisol response to the TSST compared to HC after placebo. After fludrocortisone, cortisol values were diminished in both conditions and across groups. sAA increased in response to stress across groups and was not affected by MR stimulation. These findings demonstrate that BPD show a blunted cortisol response to stress. Because negative feedback through exogenous MR stimulation leads to comparable cortisol values in BPD and HC, these findings make it less likely that increased MR-mediated feedback is the primary mechanism underlying the blunted cortisol response to stress in BPD.

Clinical trials registration: [ClinicalTrials.gov](https://clinicaltrials.gov) ID: NCT05310253

1. Introduction

Borderline personality disorder (BPD) is characterized by affective instability, impulsivity, rapidly changing mood as well as stress related anger and dissociation (American Psychiatric Association, 2013; Lazarus et al., 2014). On a biological level, alterations in the hypothalamic-pituitary-adrenal (HPA) axis activity have been repeatedly reported. BPD has been associated with elevated basal cortisol secretion (Drews et al., 2019), but a blunted or absent cortisol response to acute

psychosocial stressors, such as the Trier Social Stress Test (TSST) has been consistently reported (Drews et al., 2019; Duesenberg et al., 2019; Ehrenthal et al., 2018; Graumann et al., 2021; Simeon et al., 2007).

Furthermore, alterations in HPA-axis feedback sensitivity have frequently been investigated but have shown inconsistent results and results of these studies are difficult to interpret due to small samples, differing test procedures, outdated diagnostic criteria, high comorbidities with MDD and the absence of control samples (Drews et al., 2019; Kulakova et al., 2024; Wingenfeld et al., 2010).

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However, there is some evidence for an enhanced feedback sensitivity particularly in patients without comorbid depression but with predominant trauma-related symptoms (Wingenfeld and Wolf, 2015). These previous studies on HPA-axis feedback regulation in BPD used dexamethasone suppression tests and, thus, focused on GR-mediated feedback mechanisms. Importantly, HPA-axis feedback regulation is mediated by two receptor types: the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR). While GRs seem to be activated at higher cortisol concentrations and contribute to slower, genomic processes, MRs seem to exhibit non-genomic effects that respond rapidly to rising cortisol levels, making them relevant for the early phase of the acute stress response (de Kloet and Joëls, 2024).

However, most of the available evidence derives from studies in rodents (Paul et al., 2022). In humans, early evidence likewise indicated that stimulation of MRs with the agonist fludrocortisone inhibits cortisol secretion (Buckley et al., 2007). Of note, MR mediated negative feedback was also observed in patients with MDD (Nowacki et al., 2020; Otte et al., 2003; Otte et al., 2015) but has not been examined in BPD. Based on these studies, fludrocortisone as an MR agonist directly activates central MRs, mimicking the effect of high circulating cortisol levels and signaling to the hypothalamus and pituitary that sufficient cortisol is available. This inhibits further corticotropin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH) release, and thereby cortisol output (Buckley et al., 2007). Pharmacological MR stimulation allows the functional responsiveness of MR-mediated feedback to be assessed, whereas MR blockade provides a complementary approach to examining the contribution of endogenous MR signaling to HPA-axis regulation (Deuter et al., 2024). However, the commonly used MR antagonist spironolactone also interacts with androgen and progesterone receptors (Sica, 2005), potentially introducing hormonal confounding in a design aimed at minimizing gonadal hormone influences.

Psychosocial stress also activates the sympathetic nervous system (SNS), frequently measured using salivary alpha-amylase (sAA) (Jones et al., 2020). MR stimulation may also affect SNS activity, as rodent studies suggest that MR activation enhances sympathetic drive (Felder, 2010; Francis et al., 2001). Evidence in humans is scarce and only available on MR blockade, which does not affect sAA responses (Cornelisse et al., 2011). Effects of MR stimulation on SNS activation have not been investigated in BPD yet. However, in response to stress findings in BPD are mixed, with some studies indicating a blunted sAA response (Duesenberg et al., 2019; Nater et al., 2010; Scott et al., 2013), which others did not observe (Graumann et al., 2021; Inoue et al., 2015).

To better understand the effects of MR function in the brain, measures of cognitive function after pharmacological MR stimulation might be promising in humans. MR stimulation with fludrocortisone improved hippocampal dependent memory in healthy individuals as well as in patients with MDD (Hinkelmann et al., 2015; Otte et al., 2015). In contrast, patients with BPD showed a different pattern with impaired declarative memory performance after fludrocortisone compared to placebo (Wingenfeld et al., 2015) but unaltered cognitive processes that are more related to prefrontal brain areas (Wingenfeld et al., 2014; Wingenfeld et al., 2015). Thus, the hypothesis arises that MR function and feedback inhibition in the hippocampus might be altered in BPD. The present study focused on biologically female participants. Including participants of other sexes while retaining the factorial design would have required a substantially larger sample, which was beyond the scope of the present trial. In addition, BPD is diagnosed more frequently in female patients than in males in clinical samples (Lieb et al., 2004). We therefore focused on female participants as a first step. The aim of the present study was to investigate the effects of single-dose MR stimulation with fludrocortisone on cortisol release to acute psychosocial stress in female patients with BPD and healthy controls. Cortisol was assessed in saliva. As a marker for the activation of the SNS we also measured sAA for exploratory purposes. After administration of fludrocortisone or placebo, participants were exposed to an acute psychosocial stress situation (Trier Social Stress Test, TSST) or to a “placebo” version of the

TSST (P-TSST). Based on previous findings, we hypothesized that after placebo, the TSST would elicit a larger cortisol response in HC than in patients with BPD. We further predicted that MR stimulation with fludrocortisone would decrease cortisol values over time, and that this reduction would be more pronounced in patients with BPD, due to enhanced feedback sensitivity. Combining fludrocortisone with psychosocial stress, we expected the typical TSST-induced cortisol increase to be suppressed in healthy controls, reflecting inhibitory feedback, and thereby reducing group differences.

2. Methods

2.1. Participants

The present study is part of a larger registered research project (ClinicalTrials.gov: NCT05310253). Salivary cortisol and alpha-amylase were included as pre-specified secondary outcome measures in the trial registration. The present article reports these neuroendocrine outcomes. The behavioral outcomes will be reported in a separate publication.

A priori sample size calculation was conducted using G*Power (Faul et al., 2009) for this larger randomized study. To find an effect of $f = 0.25$ with $\alpha = 0.05$ and power $(1-\beta) = 0.90$ a total sample of 232 is needed (rmANOVA, four measurement points, eight groups). The effect size was based on previous studies investigating cortisol responses to stress in BPD and to MR stimulation (Drews et al., 2019; Nowacki et al., 2020). Thus, we decided to recruit 30 patients with BPD and 30 healthy controls per condition (total $N = 240$).

120 female patients with BPD and 120 healthy controls (HC), between 18 and 60 years, participated in the study. We focused on biologically female participants (sex assigned at birth). Gender identity was not assessed. General exclusion criteria included a body mass index (BMI) below 17.5 or above 30, glucocorticoid intake, pregnancy, and any autoimmune, metabolic, neuroendocrine, neurodegenerative, central nervous system (CNS), or other severe somatic diseases. HC had no current or past mental disorders. Exclusion criteria for patients with BPD were lifetime psychotic symptoms, current substance addiction, acute suicidality, current major depression, use of benzodiazepines, and current intake of more than three psychotropic medications. Medication dosages were stable for at least one week prior to testing. HC and BPD were matched for age, education, menstrual cycle phase and hormonal contraceptive (yes/no). Recruitment was conducted via online postings and hospital flyers at the Department of Psychiatry and Neurosciences, Charité – Universitätsmedizin Berlin. Participants were reimbursed with €65. Participants were diagnosed by trained clinicians using the Structured Clinical Interview for DSM-5 Disorders (SCID) (German versions of SCID-5-CV, SCID-5-PD; Beesdo-Baum et al., 2019). Self-reported severity of borderline symptoms were assessed with the short version of the Borderline Symptom List (BSL-23) (Bohus et al., 2008). Self-reported symptoms of posttraumatic stress disorder (PTSD) were assessed via the German version (Christen et al., 2021) of the International Trauma Questionnaire (ITQ) (Cloitre et al., 2018). All participants gave written informed consent. The study was approved by the Ethics Committee at Charité and conducted in line with the declaration of Helsinki.

2.2. Procedure

Sessions took place between 13:00 and 17:00 to minimize the impact of circadian hormone fluctuation. Stress was induced using the Trier Social Stress Test (TSST), a standardized laboratory stressor that reliably elicits cortisol responses in healthy individuals (Kirschbaum et al., 1993). It consists of a 5-min preparation phase, followed by a 5-min job application speech and a 5-min arithmetic task (serial subtraction of 13 from 2083), performed in front of an evaluating panel consisting of two members (one female, one male). A “Placebo” version of the TSST (pTSST) served as the control condition (Het et al., 2009). In the pTSST,

participants spoke aloud about a neutral topic of their choice (e.g., a book or travel experience) in an empty room, followed by an easy counting task (counting in multiples of 15), after the same preparation period.

120 min before the (p)TSST, we administered 0.4 mg fludrocortisone or placebo via identical looking pills. Fludrocortisone is a mineralocorticoid receptor agonist, of which the peak plasma levels occur approximately 1.7 h after oral administration (Vogt et al., 1971). Participants were randomly assigned to one of four double-blind conditions: (1) Placebo (P) + pTSST, (2) Placebo (P) + TSST, (3) Fludrocortisone (Flu) + TSST, or (4) Fludrocortisone (Flu) + pTSST. A computer-generated randomization list was prepared and implemented by an independent researcher, ensuring that experimenters were blind to allocation and that group sizes were approximately equal across conditions (30 patients with BPD and 30 healthy controls per condition). During the waiting period between drug administration and the (p)TSST, participants completed a set of self-report questionnaires. Mood, wakefulness, and nervousness were assessed using the Multidimensional Mood State Questionnaire (MDMQ; (Steyer et al., 1997)) before the (p)TSST (T1), after the (p)TSST (T2), and one hour after (p)TSST (T3).

Saliva samples were collected using SaliCap devices (IBL, Hamburg, Germany) at four time points: baseline at 0 min (T0), immediately before the (p)TSST at +120 min (T1) and after (p)TSST at +135 (T2) and + 195 (T3) min. Samples were stored at -80°C until biochemical analyses in the Neurobiology Laboratory of the Department of Psychiatry and Neuroscience, Charité, Universitätsmedizin Berlin. Free cortisol was analyzed using an adapted homogenous time-resolved fluorescence resonance energy transfer (HTR-FRET)-based competitive immunoassay. Intra-assay coefficients of variation were below 8%, inter-assay coefficients of variation were below 10%. The limit of detection of free cortisol was 0.2 nM. All samples and standards were measured in duplicates. Alpha-amylase activity was determined using a modified protocol of a previously published direct alpha-amylase assay (Lorentz et al., 1999). Inter- and intra-assay coefficients of variation were both lower than 10%. All samples and standards were measured in triplicates.

Statistical analyses were conducted using SPSS version 30. Demographics were analyzed using *t*-tests (continuous variables) and chi-square tests (categorical variables). MDMQ data were analyzed using rm-ANOVA with time (T1, T2, T3) as within-subject factor, and group (BPD vs. HC) and condition (P + pTSST, P + TSST, Flu + TSST, Flu + pTSST) as between-subject factors. Significant interaction effects were followed up using Bonferroni-corrected simple effects analyses and pairwise comparisons. Reported change scores (Δ) reflect T1–T2 differences based on the estimated marginal means. Salivary cortisol and alpha-amylase were analyzed using repeated-measures (rm) ANOVA with time (T0, T1, T2, T3) as within-subject factor, and group (BPD vs. HC) and condition (P + pTSST, P + TSST, Flu + TSST, Flu + pTSST) as between-subject factors. Cortisol and alpha-amylase values were log-transformed. Significant interaction effects were further examined using Bonferroni-corrected repeated-measures and univariate ANOVAs, with follow-up pairwise comparisons reported in the results.

3. Results

3.1. Demographic data

There were no significant differences between groups in age, years of education, body mass index (BMI), menstrual cycle phase, or contraceptive use. However, a higher proportion of participants in the BPD group were smokers ($p < .001$). As expected, patients with BPD reported significantly higher scores on the BSL-23 ($p < .001$) (Table 1).

3.2. Mood (MDMQ)

On the MDMQ subscale mood (good/bad), we found a significant

Table 1

Sample characteristics and psychopathology questionnaire data.

Variable	BPD $n = 120$	HC $n = 120$	Statistics
Age (M/SD)	25.85 (6.20)	25.73 (5.80)	$t(238) = -0.14, p = .89$
Years of school education (M/SD)	11.83 (1.54)	12.09 (0.99)	$t(238) = 1.54, p = .12$
Smoker (y/n)	(62/58) (52%/48%)	(8/112) (7%/93%)	$\chi^2(1) = 58.81, p < .001^{**}$
Body mass index (M/SD)	22.32 (3.15)	22.29 (2.67)	$t(238) = -0.07, p = .94$
Natural cycle phase (follicular/luteal/no natural cycle*)	(43/45/32)	(51/44/25)	$\chi^2(2) = 1.55, p = .46$
Hormonal contraceptive (y/n)	(24/96)	(21/99)	$\chi^2(1) = 0.25, p = .62$
BSL-23 (M/SD)	2.04 (0.87)	0.10 (0.17)	$t(166.88) = -24.05, p < .001^{**}$

Note. BPD borderline personality disorder, HC healthy controls, n sample size, M Mean, SD standard deviation, y yes, n no, BSL-23 Borderline Symptom List-short version.

* Participants using hormonal contraceptives were included in the 'no natural cycle' category.

** BPD > HC.

effect of time, time $\times$ group, and time $\times$ condition interaction (all $ps < 0.001$). A significant time $\times$ group $\times$ condition interaction was also observed ($p = .003$). Additionally, there were significant main effects of group ($p < .001$) and condition ($p = .006$). The group $\times$ condition interaction was not significant ($p = .812$). A stress-induced decrease in mood from T1 to T2 was observed in both TSST conditions (all $ps < 0.001$), but not in the pTSST conditions (all $ps > 0.05$). This decrease during P + TSST was more pronounced in BPD ($\Delta = 5.47$) than in HC ($\Delta = 2.37$), resulting in the largest group difference at stress peak (T2; $\Delta M = 6.00, p < .001$). On the subscale calmness (calm/nervous), there was also a significant effect of time, time $\times$ group, and time $\times$ condition interaction (all $ps \leq 0.001$). A significant time $\times$ group $\times$ condition interaction was also observed ($p = .022$). Additionally, there were significant main effects of group ($p < .001$) and condition ($p = .008$). The group $\times$ condition interaction was not significant ($p = .480$). Calmness decreased more strongly during P + TSST in BPD ($\Delta = 5.57$) than in HC ($\Delta = 3.50$), resulting in the largest group difference at stress peak (T2; $\Delta M = 6.17, p < .001$). The significant time $\times$ group $\times$ condition interactions for mood and calmness were not driven by fludrocortisone, as both did not differ between fludrocortisone and placebo TSST conditions at stress peak or one hour post-stress (all $ps > 0.05$). On the subscale wakefulness (awake/tired) we found a significant effect of time ($p < .001$) and a significant main effect of group ($p < .001$). Full statistics on the MDMQ are reported in Table S1. Overall, patients with BPD reported feeling more tired than HC. No other significant effects were observed.

In sum, BPD reported a stronger decrease in mood and calmness in response to the TSST than HC, indicating a stronger subjective affective response to stress. For detailed statistics see supplementary material. Results for mood and calmness are presented in Fig. 1.

3.3. Physiological data

3.3.1. Cortisol

Cortisol data were available for 234 participants ($n = 116$ BPD, $n = 118$ HC). Two HC and four patients with BPD were excluded due to missing data. For cortisol, we found a significant effect of time ($F(3, 678) = 48.84, p < .001, \eta^2 = 0.18$), a significant time $\times$ group ($F(3, 678) = 10.46, p < .001, \eta^2 = 0.04$) and time $\times$ condition interaction ($F(9, 678) = 13.45, p < .001, \eta^2 = 0.15$). The interaction of time $\times$ group $\times$ condition was not significant ($F(9, 678) = 1.53, p = .13$). Additionally, there was a significant main effect of condition ($F(3, 226) = 4.72, p = .003, \eta^2 = 0.06$) and a significant group $\times$ condition interaction ($F(3,$

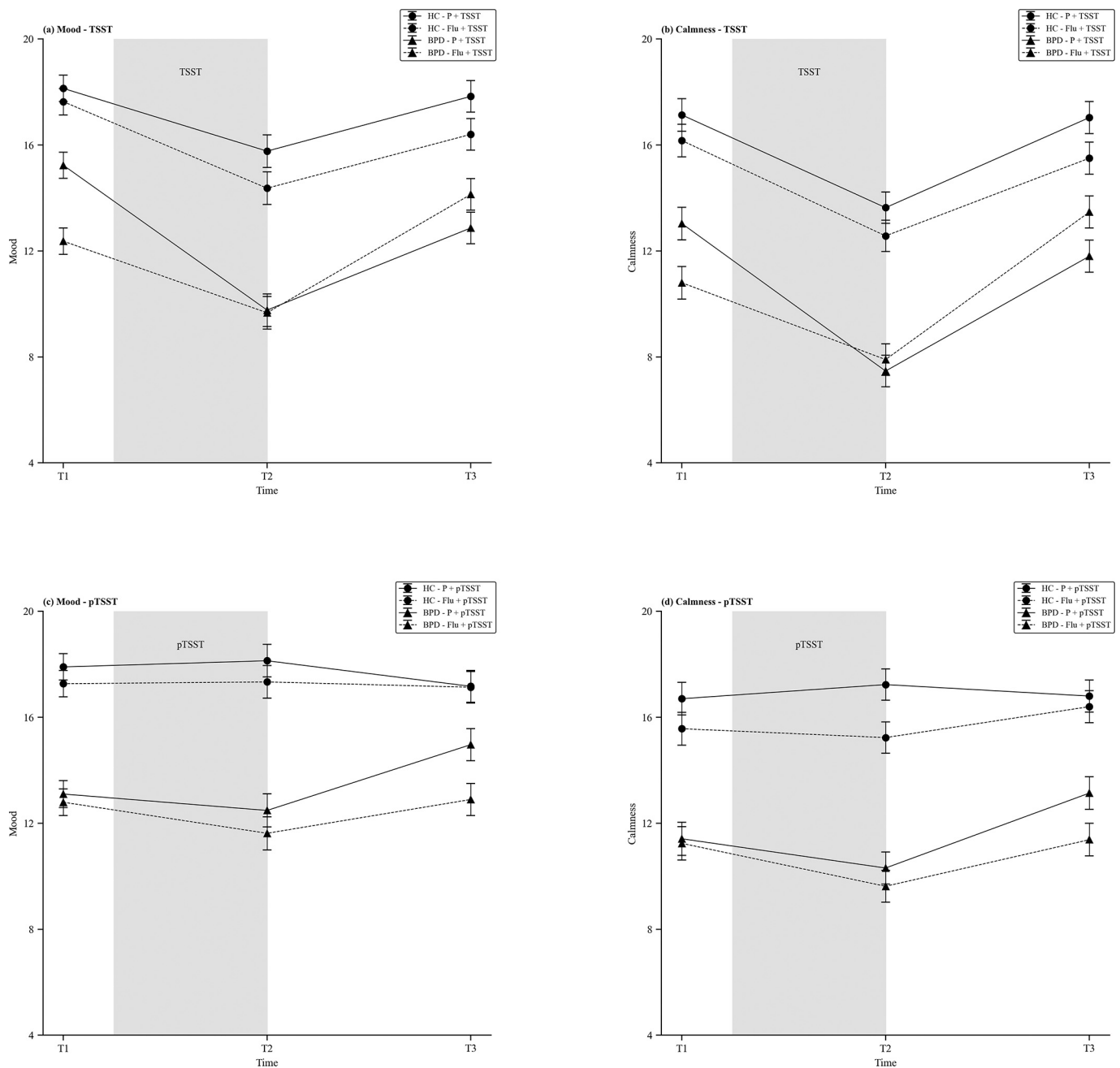


Fig. 1. MDMQ mood (good/bad) and calmness (calm/nervous) scores at three time points: before stress (T1), immediately after the (p)TSST (T2), and one hour after (p)TSST (T3): (a) Mood, TSST conditions, (b) Calmness, TSST conditions, (c) Mood, pTSST conditions, (d) Calmness, pTSST conditions, comparing groups (BPD vs. HC). The shaded areas indicate the (p)TSST periods. Higher values indicate more positive mood and greater calmness.

226) = 4.62, $p = .004$, $\eta^2 = 0.06$). Results are presented in Fig. 2 a – d.

To analyze these interactions, we performed three lines of post-hoc tests (all Bonferroni corrected): First, separate repeated-measures ANOVAs were conducted for each condition (P + TSST, P + pTSST, Flu + TSST, Flu + pTSST). In these analyses, time (T0, T1, T2, T3) was included as a within-subjects factor, and group (BPD, HC) as a between-subjects factor. In a second step, four separate univariate ANOVAs were conducted (one per sampling point), with group (BPD vs. HC) as the between-subjects factor, collapsed across conditions. Thirdly, we compared the experimental conditions across groups (one ANOVA per sampling point).

Time, group, and interaction effects per condition

In the P + TSST condition there was a significant time $\times$ group interaction ($F(3,174) = 6.52$, $p < .001$, $\eta^2 = 0.10$), with lower cortisol

values in BPD compared to HC immediately after stress (T2; $p = .011$) and one-hour post stress (T3; $p < .001$). In the P + pTSST there was a significant time effect ($F(3,162) = 19.61$, $p < .001$, $\eta^2 = 0.27$). Although this may partly reflect the circadian decline in cortisol during the afternoon, the observed decline might also reflect recovery from anticipatory arousal associated with arriving at an unfamiliar testing facility.

In both fludrocortisone conditions a significant effect of time was observed (all $ps < 0.001$), indicating a decrease in cortisol values following fludrocortisone administration. Furthermore, in the Flu + pTSST the group effect also became significant ($F(1,57) = 8.65$, $p = .005$, $\eta^2 = 0.13$), reflecting higher cortisol in the patients group. Full statistics are reported in Table S2.

Group differences per time point

Comparing BPD patients with healthy controls (across conditions) at

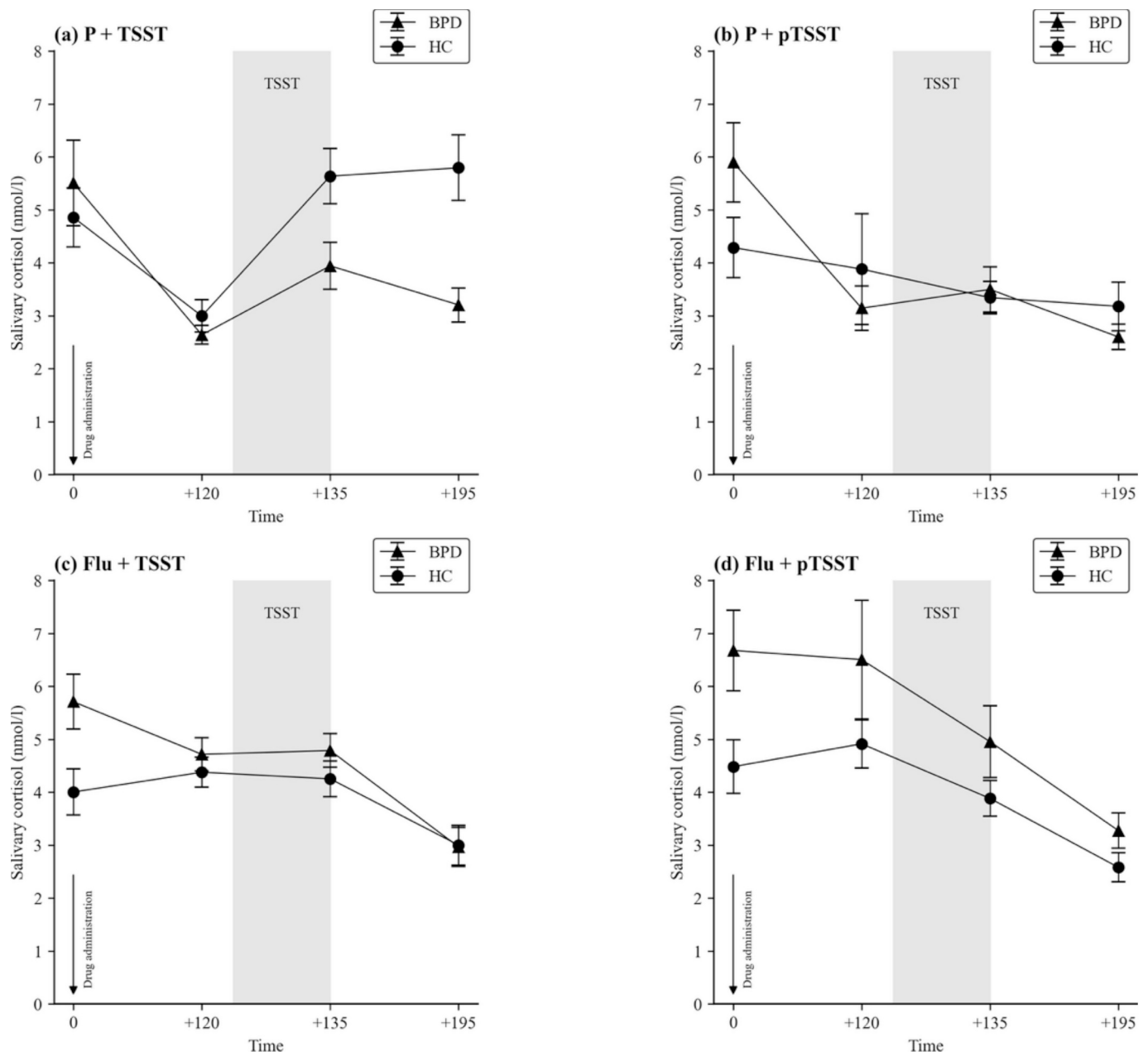


Fig. 2. Mean ($\pm$ SEM) salivary cortisol (nmol/l) at four sampling points: baseline at T0, immediately before the (p)TSST at +120 min (T1), and after (p)TSST at +135 (T2) and +195 (T3) min: (a-d) group comparisons (BPD vs. HC) for each condition: (a) Placebo + TSST, (b) Placebo + pTSST, (c) Fludrocortisone + TSST, (d) Fludrocortisone + pTSST.

each measurement point revealed the following results: At T0 there was significant effect of group ($F(1, 236) = 14.06, p < .001, \eta^2 = 0.06$), with pairwise comparisons indicating that BPD had significantly higher baseline cortisol values than HC ($p < .001$). There were no significant main effects of group at T1 ($p = 1.00$), T2 ($p = 1.00$), and T3 ($p = .113$).

Condition differences per time point

Comparing experimental conditions (across groups) at each measurement point revealed the following results: At baseline there were no significant differences in cortisol values between conditions ($p = .58$). Cortisol values differed significantly between conditions at T1 ($p < .001$), T2 ($p < .007$) and T3 ($p < .001$). At T1, pairwise comparisons indicated that in both placebo conditions, cortisol values were significantly lower than in both fludrocortisone conditions (all $ps < 0.001$). No significant differences were observed between the two placebo conditions or between the two fludrocortisone conditions (all $ps > 0.01$). At

T2, cortisol values were lowest in the P + pTSST condition and differed significantly from the Flu + TSST condition ($p = .004$). The other three conditions (Flu + TSST, Flu + pTSST, P + TSST) did not differ from each other. At T3, cortisol values in the P + TSST condition were higher compared to P + pTSST ($p = .001$) and Flu + TSST ($p = .006$), and at trend level compared to Flu + pTSST ($p = .017$), i.e., cortisol values in the fludrocortisone conditions seem to have returned to baseline earlier. Thus, the main result from these analyses is that fludrocortisone inhibits the cortisol increase, including the response to stress.

In sum, female patients with BPD exhibited a blunted cortisol response to stress in the placebo condition and showed elevated baseline cortisol values at T0. Fludrocortisone administration inhibited cortisol secretion, resulting in comparable cortisol values between patients with BPD and healthy controls. Exploratory analyses, including medication status as a covariate as well as comparing medicated and unmedicated

patients with BPD, indicated that psychotropic medication did not impact the cortisol results (see supplementary material). Since patients with BPD smoked more than HC, we also conducted an exploratory sensitivity analysis within the BPD group. Within the BPD group, the time $\times$ condition $\times$ smoking interaction was not significant ($F(7.11, 256.06) = 1.52, p = .159, \eta^2 = 0.041$). However, there was a significant time $\times$ smoking interaction ($F(2.37, 256.06) = 4.48, p = .008, \eta^2 = 0.040$), and within the placebo + TSST condition an exploratory analysis indicated a smaller stress-induced cortisol increase in patients who smoked ($F(1.98, 55.36) = 6.37, p = .003, \eta^2 = 0.185$). Full sensitivity analyses are reported in the supplementary material.

3.4. Salivary α -Amylase (sAA)

Alpha-Amylase data were available for 235 participants ($n = 118$

BPD, $n = 117$ HC). Three HC and two patients with BPD were excluded due to missing data. For sAA we found a main effect of time ($F(3, 690) = 38.44, p < .001, \eta^2 = 0.14$). We also found a significant time $\times$ condition interaction ($F(9, 681) = 3.22, p < .001, \eta^2 = 0.04$). To analyze the time $\times$ condition interaction, four separate, Bonferroni corrected univariate ANOVAs were conducted (one for each sampling point), with condition (P + pTSST, P + TSST, Flu + pTSST, Flu + TSST) as the between-subjects factor, collapsed across groups. sAA values differed significantly between conditions (Fig. 3a-d) immediately after the (p)TSST (T2) ($F(3, 233) = 3.72, p = .012, \eta^2 = 0.05$), suggesting an increase in sAA after the TSST ($ps < 0.05$). However, none of the pairwise comparisons between conditions survived Bonferroni correction for multiple testing. There were no differences between conditions at T0 min ($F(3, 233) = 0.91, p = .44$), T1 ($F(3, 233) = 1.42, p = .24$), or at T3 ($F(3, 233) = 0.47, p = .71$).

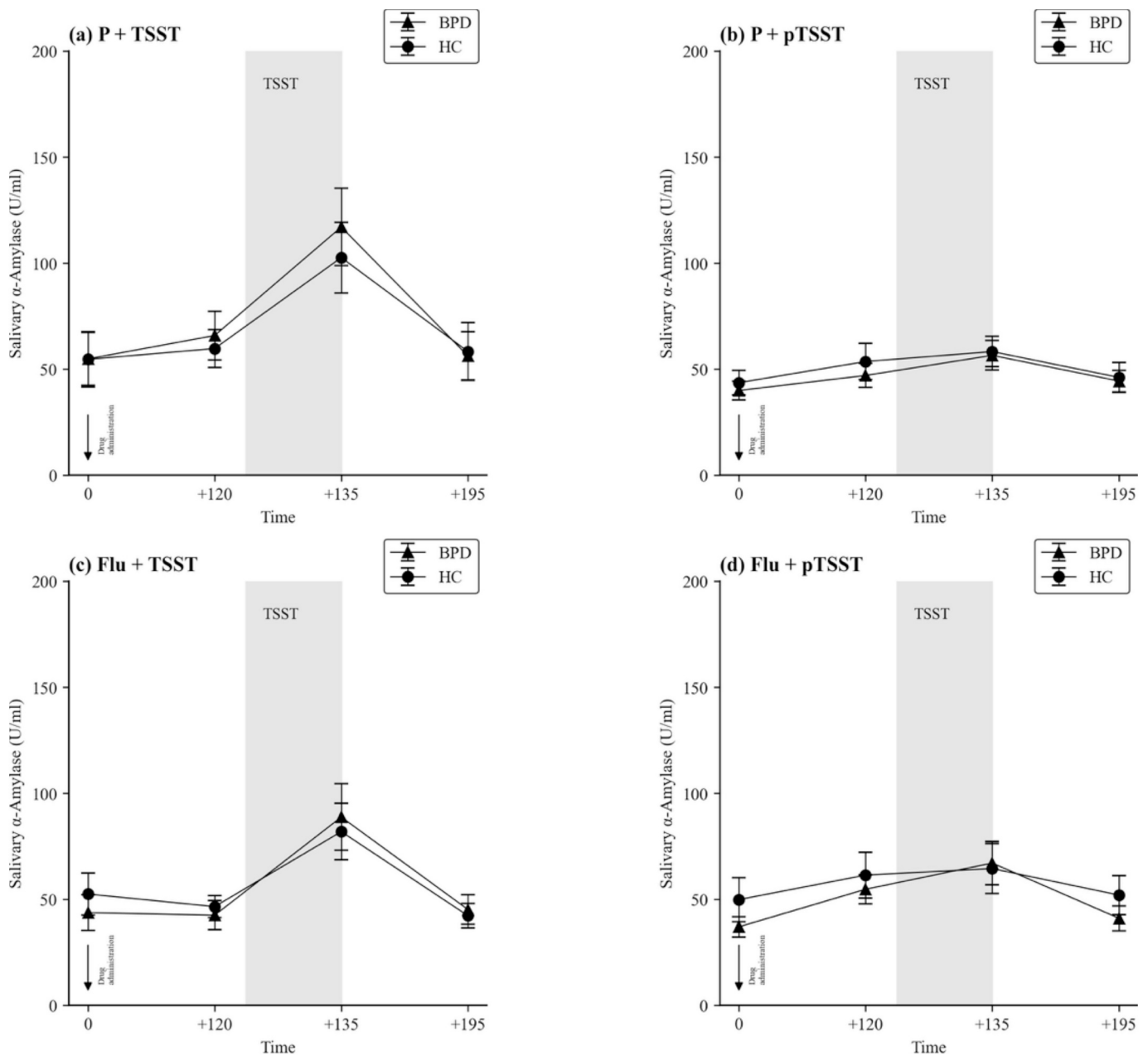


Fig. 3. Mean ($\pm$ SEM) salivary α -Amylase (U/ml) at four sampling points: baseline at T0, immediately before the (p)TSST at +120 min (T1), and after (p)TSST at +135 (T2) and +195 (T3) min: (a-d) group comparisons (BPD vs. HC) for each condition: (a) Placebo + TSST, (b) Placebo + pTSST, (c) Fludrocortisone + TSST, (d) Fludrocortisone + pTSST.

4. Discussion

This study investigated the effects of acute mineralocorticoid receptor stimulation using fludrocortisone on salivary cortisol responses to the TSST and its placebo version in female patients with BPD and healthy controls. Salivary alpha-amylase was measured for exploratory purposes. We replicated earlier findings of a blunted cortisol response to stress in patients with BPD compared to HC, despite patients reporting a higher subjective affective response to stress than controls. At baseline, cortisol values were higher in the BPD group than in HC. After stimulation with fludrocortisone, there was no cortisol increase to stress in HC and BPD and cortisol values decreased continuously until the end of the study. Across both groups, sAA increased in response to stress, and fludrocortisone did not appear to impact this response.

The elevated cortisol values in BPD at laboratory arrival, i.e. before drug administration, are in line with other studies reporting higher basal cortisol in BPD (Drews et al., 2019). However, since group differences were no longer evident immediately before the TSST, this seems to reflect a transient anticipatory elevation rather than a stable change in basal cortisol release. Of note, meta-analytic evidence for enhanced cortisol values in BPD in singular assessment is weak and triggered by outlier studies (Drews et al., 2019).

Our finding of a blunted cortisol response to acute stress in BPD is consistent with the majority of previous studies (Drews et al., 2019; Duesenberg et al., 2019; Ehrenthal et al., 2018; Scott et al., 2013). One factor that may contribute to this pattern is early adversity, BPD has a high rate of early childhood trauma and in these individuals and a blunted cortisol response to stress has been found, repeatedly (Bunea et al., 2017; Lovallo et al., 2012). In addition, we found that patients with PTSD (due to childhood trauma) also showed a blunted cortisol response to stress (Metz et al., 2020). Early adversity may therefore contribute to the observed blunted cortisol response not only in BPD but trans-diagnostically. The biological mechanism underlying this blunted response is not yet clear, but altered negative feedback regulation of the HPA-axis, possibly in concert with increased corticotropin-releasing factor (CRF) activity and subsequent enhanced basal cortisol release, has been discussed (Heim et al., 2008; Wingenfeld et al., 2010).

Notably, in line with one of our former studies (Duesenberg et al., 2019), the blunted cortisol response in BPD occurred despite a higher subjective affective response to stress compared to healthy controls. A comparable dissociation has been reported in children and adolescents with a history of maltreatment, who showed a blunted cortisol response to an age-adapted version of the TSST alongside greater perceived anxiety (Marques-Feixa et al., 2023) suggesting that early adversity may contribute to this pattern trans-diagnostically. Studies involving cortisol administration, as well as studies examining endogenous cortisol responses, suggest that cortisol may attenuate negative affect and facilitate emotion regulation following acute stress (Het et al., 2012; Het and Wolf, 2007; Langer et al., 2025). Therefore, the dissociation between heightened subjective affective response to stress and a blunted cortisol response in BPD in our study could be interpreted as reflecting reduced cortisol-mediated buffering of negative affect.

The major finding of our study is that MR stimulation with fludrocortisone inhibits cortisol release in response to acute psychosocial stress in HC and BPD. As MR-mediated feedback seems primarily relevant for the early phase of the acute stress response, we hypothesized that MR stimulation with fludrocortisone would attenuate the stress-induced increase in cortisol in HC, which is in line with the results of the present study. MR stimulation appeared to promote a decline in cortisol values over time, i.e. end of the study day at 195 min after fludrocortisone intake. Overall, our finding align with previous work in rodents and humans showing that MR activation inhibits cortisol release (Paul et al., 2022) and extend these findings by demonstrating that MR plays a key role in regulating cortisol release after a psychosocial stressor. The observed effect seems consistent with central MR-dependent feedback mechanisms (Paul et al., 2022). As MR-mediated

HPA-axis regulation in humans has been proposed to involve limbic structures such as the hippocampus, hippocampal MR signaling provides a plausible mechanistic framework for the present findings (Le Menuet and Lombès, 2014; Watzka et al., 2000). However, our design does not allow the underlying neuroanatomical mechanisms to be determined, and a contribution of pituitary MR cannot be excluded.

With respect to BPD, we hypothesized that this reduction in cortisol release in response to the stressor would be more pronounced in patients with BPD, due to enhanced feedback sensitivity. However, our findings indicate that MR stimulation did not reveal altered MR-mediated feedback in BPD. Fludrocortisone suppressed cortisol in patients with BPD, suggesting that MRs in our BPD sample are able to mediate negative feedback inhibition of the HPA axis with no difference from HC. This makes it less likely that the blunted cortisol response to stress observed in BPD primarily reflects enhanced MR-mediated negative feedback during acute stress. An alternative mechanism may involve GR-mediated feedback. In contrast to MRs, GRs are increasingly recruited at higher cortisol concentrations and contribute to termination and recovery of the stress response (de Kloet and Joëls, 2024). Thus, enhanced GR-mediated feedback could potentially contribute to a blunted cortisol response in BPD, possibly in concert with an altered MR/GR balance (Paul et al., 2022). However, findings on GR-mediated feedback sensitivity in BPD are heterogeneous with dexamethasone suppression tests showing enhanced as well as reduced sensitivity (Wingenfeld et al., 2010). Evidence consistent with potentially reduced GR sensitivity also comes from molecular studies, with increased methylation of the GR receptor gene reported in BPD (Dammann et al., 2011) and methylation status and severity of borderline symptoms and childhood trauma were positively correlated in another study (Martín-Blanco et al., 2014). In contrast, enhanced GR-mediated feedback sensitivity has been reported in individuals with childhood trauma and PTSD, as well as in patients with BPD (Heim et al., 2008; Ressler et al., 2022; Rinne et al., 2002; Yehuda et al., 2015).

However, the present study specifically assessed MR-mediated negative-feedback sensitivity in response to pharmacological MR stimulation, whereas other aspects of MR function in BPD remain insufficiently understood. In this context, we have measured mRNA expression of the GR and MR on peripheral blood-derived mononuclear cells but did not find alterations in women with a history of childhood trauma (Hellmann-Regen et al., 2019). To better understand the effects of GR and MR function in the brain, measures of cognitive function after pharmacological stimulation are frequently used and might give indirect evidence for its function. Specifically, after hydrocortisone administration, i.e. simultaneous stimulation of MR and GR, improved memory retrieval was found in patients with BPD but not in healthy individuals, whereas executive functions, which are less dependent on hippocampal processing, were unaffected. This pattern points to a preferential effect on hippocampus-dependent processes. In contrast, after fludrocortisone administration, we found an opposite pattern with impaired verbal and visuospatial memory. This was again different from results in a healthy control group (results are summarized in Wingenfeld and Otte, 2019; Wingenfeld and Wolf, 2015). Thus, hippocampus-dependent memory effects in BPD may depend on GR co-activation or the balance between MR and GR activation rather than on MR stimulation alone. Taken together our current findings and these previous studies suggest that further investigation is needed on whether hippocampal mediated feedback regulation involving GR function, potentially in interaction with MR signaling, contributes to the reduced cortisol response to psychosocial stress in BPD.

The sympathetic nervous system was not the primary scope of the study, but sAA was assessed on an explorative basis. SAA was increased in response to stress across both groups, indicating unaltered sympathetic activation in BPD, which is in line with several other studies (Graumann et al., 2021; Inoue et al., 2015). Interestingly, sAA did also not differ between groups at arrival, suggesting that the elevation in cortisol was selective to the HPA-axis rather than reflecting a

generalized biological arousal. This pattern is consistent with models proposing partially independent regulation of HPA-axis and sympathetic stress responses (Jones et al., 2020). Fludrocortisone administration affected the HPA-axis but did not alter sAA responses. This pattern is complementary to previous findings showing that MR blockade likewise did not impact sAA, supporting the specificity of MR effects for endocrine rather than sympathetic stress systems (Cornelisse et al., 2011).

To our knowledge, this is the first study to investigate the effects of MR stimulation on stress-induced cortisol responses in healthy individuals and patients with BPD. Strengths include the robust randomized, placebo-controlled, double-blind design, a relatively large and tightly matched sample, controlled menstrual phase and contraceptive use, and exclusion of MDD patients to minimize confounding. Additionally, we excluded individuals undergoing gender-affirming hormone therapy due to its effects on HPA-axis function. Therefore, the generalizability of our results to transgender individuals with BPD is limited. As the present study focused on biologically female individuals, findings may not generalize to male individuals with BPD. Furthermore, gender identity was not assessed, which may limit the generalizability to gender-diverse individuals with BPD. The initial sample size was calculated using a global rmANOVA medium effect of $f = 0.25$ and may not have been large enough to detect very small time-by-group-by-condition differences. The number of saliva sampling points was also limited, which might result in a loss of information regarding cortisol dynamics during the 120-min waiting period and in the phase following the (p)TSST. Sampling at T2 occurred 15 min after onset of the (p)TSST, which is earlier than other commonly used TSST protocols. Further rises in cortisol levels might thus not be captured by our measure. As sampling was identical across conditions and groups, the comparisons between conditions still hold, and our primary focus was on the TSST-induced cortisol increase. Patients with BPD were partly medicated while healthy controls were not. Our exploratory analyses provided no evidence that psychotropic medication influenced the cortisol results, neither as a covariate across the whole sample nor when comparing medicated and unmedicated patients within the BPD group. However, an impact of medication cannot be entirely ruled out, since condition-specific comparisons between medicated and unmedicated patients were not sufficiently powered. Similarly, smoking status was confounded with group, and habitual smoking has been shown to attenuate HPA-axis responsiveness to psychological stress (Rohleder and Kirschbaum, 2006). Exploratory analyses within the BPD group indicated a smaller stress-induced cortisol increase in patients who smoked, although these were based on small subsamples and should therefore be interpreted with caution. Smoking may have partly contributed to the blunted cortisol response observed. However, blunted stress reactivity has been proposed as a risk marker that may precede substance use, as it is also observed in vulnerable individuals who have not developed a substance use disorder (al'Absi et al., 2021). Therefore, smoking may represent one expression of a shared developmental pathway rather than an independent influence. Its contribution cannot be disentangled from diagnostic group in the present sample.

Finally, childhood trauma is common in BPD and has been associated with blunted cortisol responses trans-diagnostically (Bunea et al., 2017). As we did not include a control group of patients with BPD without a history of childhood trauma, we cannot determine whether the blunted cortisol response observed here is specific to BPD or reflects early childhood trauma as a transdiagnostic risk factor for a blunted cortisol response to stress. Including such a group in future research would help to disentangle the two. Future studies should also include male and gender-diverse participants and assess gender identity. In addition, incorporating denser saliva sampling would allow a more detailed investigation of cortisol dynamics following MR stimulation. Finally, future work should assess glucocorticoid receptor function during acute stress. In summary, our study shows that acute MR stimulation with fludrocortisone attenuated cortisol responses to psychosocial stress in both female patients with BPD and HC, indicating that MR activation

promotes rapid HPA-axis regulation. Our findings provide evidence that exogenous MR stimulation does not alter MR-mediated feedback in female patients with BPD.

CRediT authorship contribution statement

Marie Barthauer: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Livia Graumann:** Writing – review & editing, Investigation, Conceptualization. **An Bin Cho:** Writing – review & editing, Conceptualization. **Eugenia Kulakova:** Writing – review & editing, Conceptualization. **Christian Eric Deuter:** Writing – review & editing, Software. **Oliver T. Wolf:** Writing – review & editing, Conceptualization. **Julian Hellmann-Regen:** Writing – review & editing, Resources. **Stefan Roepke:** Writing – review & editing, Conceptualization. **Christian Otte:** Writing – review & editing, Conceptualization. **Katja Wingenfeld:** Writing – review & editing, Methodology, Funding acquisition.

Consent for publication

All participants including patients were informed about the study orally and in written form and had to give written consent before participating. Participants signed informed consent regarding publishing their data.

Ethical approval and consent to participate

The Charité ethics committee approved this study. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jad.2026.122552>.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials. Further data are available from the corresponding author (KW) upon reasonable request.

References

- al'Absi, M., Ginty, A.T., Lovallo, W.R., 2021. Neurobiological mechanisms of early life adversity, blunted stress reactivity and risk for addiction. *Neuropharmacology* 188, 108519.
- American Psychiatric Association, 2013. *Diagnostic and Statistical Manual of Mental Disorders*, 5 ed. American Psychiatric Association.
- Beesdo-Baum, K., Zaudig, M., First, M.B., Wittchen, H.U., 2019. SCID-5-PD: Strukturiertes Klinisches Interview für DSM-5-Persönlichkeitsstörungen. J. B. W. W. Deutsche Bearbeitung des Structured Clinical Interview for DSM-5—personality disorders von Michael B. First, Lorna Smith Benjamin, Robert L. Spitzer, Trans.. Hogrefe.
- Bohus, M., Kleindienst, N., Limberger, M.F., Stieglitz, R.-D., Domsalla, M., Chapman, A. L., Steil, R., Philipsen, A., Wolf, M., 2008. The short version of the borderline

- symptom list (BSL-23): development and initial data on psychometric properties. *Psychopathology* 42 (1), 32–39. <https://doi.org/10.1159/000173701>.
- Buckley, T.M., Mullen, B.C., Schatzberg, A.F., 2007. The acute effects of a mineralocorticoid receptor (MR) agonist on nocturnal hypothalamic–adrenal–pituitary (HPA) axis activity in healthy controls. *Psychoneuroendocrinology* 32 (8–10), 859–864.
- Bunea, I.M., Szentágotai-Táti, A., Miu, A.C., 2017. Early-life adversity and cortisol response to social stress: A meta-analysis. *Transl. Psychiatry* 7 (12), 1274.
- Christen, D., Killikelly, C., Maercker, A., Augsburger, M., 2021. Item response model validation of the German ICD-11 international trauma questionnaire for PTSD and CPTSD. *Clinical Psychology in Europe* 3 (4), e5501.
- Cloitre, M., Shevlin, M., Brewin, C.R., Bisson, J.L., Roberts, N.P., Maercker, A., Karatzias, T., Hyland, P., 2018. The international trauma questionnaire: development of a self-report measure of ICD-11 PTSD and complex PTSD. *Acta Psychiatr. Scand.* 138 (6), 536–546.
- Cornelisse, S., Joëls, M., Smeets, T., 2011. A randomized trial on mineralocorticoid receptor blockade in men: effects on stress responses, selective attention, and memory. *Neuropsychopharmacology* 36 (13), 2720–2728.
- Dammann, G., Teschler, S., Haag, T., Altmüller, F., Tuzek, F., Dammann, R.H., 2011. Increased DNA methylation of neuropsychiatric genes occurs in borderline personality disorder. *Epigenetics* 6 (12), 1454–1462.
- de Kloet, E.R., Joëls, M., 2024. The cortisol switch between vulnerability and resilience. *Mol. Psychiatry* 29 (1), 20–34.
- Deuter, C.E., Kaczmarczyk, M., Hellmann-Regen, J., Kuehl, L.K., Wingenfeld, K., Otte, C., 2024. The influence of pharmacological mineralocorticoid and glucocorticoid receptor blockade on the cortisol response to psychological stress. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 129, 110905. <https://doi.org/10.1016/j.pnpbp.2023.110905>.
- Drews, E., Fertuck, E.A., Koenig, J., Kaess, M., Arntz, A., 2019. Hypothalamic-pituitary-adrenal axis functioning in borderline personality disorder: a meta-analysis. *Neurosci. Biobehav. Rev.* 96, 316–334.
- Duesenberg, M., Wolf, O.T., Metz, S., Roepke, S., Fleischer, J., Elias, V., Renneberg, B., Otte, C., Wingenfeld, K., 2019. Psychophysiological stress response and memory in borderline personality disorder. *Eur. J. Psychotraumatol.* 10 (1), 1568134. <https://doi.org/10.1080/20008198.2019.1568134>.
- Ehrental, J.C., Levy, K.N., Scott, L.N., Granger, D.A., 2018. Attachment-related regulatory processes moderate the impact of adverse childhood experiences on stress reaction in borderline personality disorder. *J. Personal. Disord.* 32 (Supplement), 93–114.
- Faul, F., Erdfelder, E., Buchner, A., Lang, A., 2009. Statistical power analyses using G* power 3.1. 9: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav. Res. Methods* 41 (4), 1149–1160.
- Felder, R.B., 2010. Mineralocorticoid receptors, inflammation and sympathetic drive in a rat model of systolic heart failure. *Exp. Physiol.* 95 (1), 19–25.
- Francis, J., Weiss, R.M., Wei, S.-G., Johnson, A.K., Beltz, T.G., Zimmerman, K., Felder, R.B., 2001. Central mineralocorticoid receptor blockade improves volume regulation and reduces sympathetic drive in heart failure. *Am. J. Phys. Heart Circ. Phys.* 281 (5), H2241–H2251.
- Graumann, L., Duesenberg, M., Metz, S., Schulze, L., Wolf, O.T., Roepke, S., Otte, C., Wingenfeld, K., 2021. Facial emotion recognition in borderline patients is unaffected by acute psychosocial stress. *J. Psychiatr. Res.* 132, 131–135.
- Heim, C., Newport, D.J., Mletzko, T., Miller, A.H., Nemeroff, C.B., 2008. The link between childhood trauma and depression: Insights from HPA axis studies in humans. *Psychoneuroendocrinology* 33 (6), 693–710.
- Hellmann-Regen, J., Spitzer, C., Kuehl, L.K., Schultebrucks, K., Otte, C., Wingenfeld, K., 2019. Altered cellular immune reactivity in traumatized women with and without major depressive disorder. *Psychoneuroendocrinology* 101, 1–6.
- Het, S., Rohleder, N., Schoofs, D., Kirschbaum, C., Wolf, O., 2009. Neuroendocrine and psychometric evaluation of a placebo version of the ‘Trier social stress test’. *Psychoneuroendocrinology* 34 (7), 1075–1086.
- Het, S., Schoofs, D., Rohleder, N., Wolf, O.T., 2012. Stress-induced cortisol level elevations are associated with reduced negative affect after stress: indications for a mood-buffering cortisol effect. *Biopsychosoc. Sci. Med.* 74 (1), 23–32.
- Het, S., Wolf, O.T., 2007. Mood changes in response to psychosocial stress in healthy young women: effects of pretreatment with cortisol. *Behav. Neurosci.* 121 (1), 11.
- Hinkelmann, K., Wingenfeld, K., Kuehl, L.K., Fleischer, J., Heuser, I., Wiedemann, K., Otte, C., 2015. Stimulation of the mineralocorticoid receptor improves memory in young and elderly healthy individuals. *Neurobiol. Aging* 36 (2), 919–924.
- Inoue, A., Oshita, H., Maruyama, Y., Tanaka, Y., Ishitobi, Y., Kawano, A., Ikeda, R., Ando, T., Aizawa, S., Masuda, K., 2015. Gender determines cortisol and alpha-amylase responses to acute physical and psychosocial stress in patients with borderline personality disorder. *Psychiatry Res.* 228 (1), 46–52.
- Jones, E.J., Rohleder, N., Schreier, H.M., 2020. Neuroendocrine coordination and youth behavior problems: a review of studies assessing sympathetic nervous system and hypothalamic-pituitary adrenal axis activity using salivary alpha amylase and salivary cortisol. *Horm. Behav.* 122, 104750.
- Kirschbaum, C., Pirke, K.-M., Hellhammer, D.H., 1993. The ‘Trier social stress test’—a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology* 28 (1–2), 76–81.
- Kulakova, E., Graumann, L., Wingenfeld, K., 2024. The hypothalamus-pituitary-adrenal axis and social cognition in borderline personality disorder. *Curr. Neuropharmacol.* 22 (3), 378–394.
- Langer, K., Wolf, O.T., Merz, C.J., Jentsch, V.L., 2025. The effects of stress hormones on cognitive emotion regulation: A systematic review and integrative model. *Neurosci. Biobehav. Rev.* 170, 106040.
- Lazarus, S.A., Cheavens, J.S., Festa, F., Rosenthal, M.Z., 2014. Interpersonal functioning in borderline personality disorder: a systematic review of behavioral and laboratory-based assessments. *Clin. Psychol. Rev.* 34 (3), 193–205. <https://doi.org/10.1016/j.cpr.2014.01.007>.
- Le Menuet, D., Lombès, M., 2014. The neuronal mineralocorticoid receptor: from cell survival to neurogenesis. *Steroids* 91, 11–19.
- Lieb, K., Zanarini, M.C., Schmahl, C., Linehan, M.M., Bohus, M., 2004. Borderline personality disorder. *Lancet* 364 (9432), 453–461.
- Lorentz, K., Gütschow, B., Renner, F., 1999. Evaluation of a Direct α -Amylase Assay Using 2-Chloro-4-Nitrophenyl- α -D-Maltotriose. *Anal. Biochem.* 265 (1), 1–5.
- Lovullo, W.R., Farag, N.H., Sorocco, K.H., Cohoon, A.J., Vincent, A.S., 2012. Lifetime adversity leads to blunted stress axis reactivity: studies from the Oklahoma family health patterns project. *Biol. Psychiatry* 71 (4), 344–349. <https://doi.org/10.1016/j.biopsych.2011.10.018>, 2012/02/15/.
- Marques-Feixa, L., Palma-Gudiel, H., Romero, S., Moya-Higueras, J., Rapado-Castro, M., Castro-Quintas, Á., Zorrilla, I., Muñoz, M.J., Ramírez, M., Mayoral, M., 2023. Childhood maltreatment disrupts HPA-axis activity under basal and stress conditions in a dose–response relationship in children and adolescents. *Psychol. Med.* 53 (3), 1060–1073.
- Martin-Blanco, A., Ferrer, M., Soler, J., Salazar, J., Vega, D., Andión, O., Sanchez-Mora, C., Arranz, M.J., Ribases, M., Feliu-Soler, A., 2014. Association between methylation of the glucocorticoid receptor gene, childhood maltreatment, and clinical severity in borderline personality disorder. *J. Psychiatr. Res.* 57, 34–40.
- Metz, S., Duesenberg, M., Hellmann-Regen, J., Wolf, O.T., Roepke, S., Otte, C., Wingenfeld, K., 2020. Blunted salivary cortisol response to psychosocial stress in women with posttraumatic stress disorder. *J. Psychiatr. Res.* 130, 112–119.
- Nater, U.M., Bohus, M., Abbruzzese, E., Ditzgen, B., Gaab, J., Kleindienst, N., Ebner-Priemer, U., Mauchnik, J., Ehrlert, U., 2010. Increased psychological and attenuated cortisol and alpha-amylase responses to acute psychosocial stress in female patients with borderline personality disorder. *Psychoneuroendocrinology* 35 (10), 1565–1572. <https://doi.org/10.1016/j.psyneuen.2010.06.002>, 2010/11/01/.
- Nowacki, J., Wingenfeld, K., Kaczmarczyk, M., Chae, W.R., Salchow, P., Abu-Tir, I., Piber, D., Hellmann-Regen, J., Otte, C., 2020. Steroid hormone secretion after stimulation of mineralocorticoid and NMDA receptors and cardiovascular risk in patients with depression. *Transl. Psychiatry* 10 (1), 109.
- Otte, C., Jahn, H., Yassouridis, A., Arlt, J., Stober, N., Maass, P., Wiedemann, K., Kellner, M., 2003. The mineralocorticoid receptor agonist, fludrocortisone, inhibits pituitary-adrenal activity in humans after pre-treatment with metyrapone. *Life Sci.* 73 (14), 1835–1845.
- Otte, C., Wingenfeld, K., Kuehl, L.K., Kaczmarczyk, M., Richter, S., Quante, A., Regen, F., Bajbouj, M., Zimmermann-Viehoff, F., Wiedemann, K., Hinkelmann, K., 2015. Mineralocorticoid receptor stimulation improves cognitive function and decreases cortisol secretion in depressed patients and healthy individuals. *Neuropsychopharmacology* 40 (2), 386–393. <https://doi.org/10.1038/npp.2014.181>, 2015/01/01.
- Paul, S.N., Wingenfeld, K., Otte, C., Meijer, O.C., 2022. Brain mineralocorticoid receptor in health and disease: from molecular signalling to cognitive and emotional function. *Br. J. Pharmacol.* 179 (13), 3205–3219.
- Ressler, K.J., Berretta, S., Bolshakov, V.Y., Rosso, I.M., Meloni, E.G., Rauch, S.L., Carlezon Jr., W.A., 2022. Post-traumatic stress disorder: clinical and translational neuroscience from cells to circuits. *Nat. Rev. Neurol.* 18 (5), 273–288.
- Rinne, T., De Kloet, E.R., Wouters, L., Goekoop, J.G., DeRijk, R.H., van den Brink, W., 2002. Hyperresponsiveness of hypothalamic-pituitary-adrenal axis to combined dexamethasone/corticotropin-releasing hormone challenge in female borderline personality disorder subjects with a history of sustained childhood abuse. *Biol. Psychiatry* 52 (11), 1102–1112.
- Rohleder, N., Kirschbaum, C., 2006. The hypothalamic–pituitary–adrenal (HPA) axis in habitual smokers. *Int. J. Psychophysiol.* 59 (3), 236–243.
- Scott, L.N., Levy, K.N., Granger, D.A., 2013. Biobehavioral reactivity to social evaluative stress in women with borderline personality disorder. *Personal. Disord. Theory Res. Treat.* 4 (2), 91.
- Sica, D.A., 2005. Pharmacokinetics and pharmacodynamics of mineralocorticoid blocking agents and their effects on potassium homeostasis. *Heart Fail. Rev.* 10 (1), 23–29.
- Simeon, D., Knutelska, M., Smith, L., Baker, B.R., Hollander, E., 2007. A preliminary study of cortisol and norepinephrine reactivity to psychosocial stress in borderline personality disorder with high and low dissociation. *Psychiatry Res.* 149 (1–3), 177–184.
- Steyer, R., Schwenkmezger, P., Notz, P., Eid, M., 1997. *Der Mehrdimensionale Befindlichkeitsfragebogen MDBF* [Multidimensional mood questionnaire]. Hogrefe. <https://doi.org/10.5160/psychdata.srrf91en15>.
- Vogt, W., Fischer, I., Ebenroth, S., Appel, S., Knedel, M., Lückner, P., Rennekamp, H., 1971. Pharmacokinetics of 9-fluorhydrocortisone. *Arzneimittelforschung* 21 (8), 1133–1143. Suppl.
- Watzka, M., Beyenburg, S., Blümcke, I., Elger, C.E., Bidlingmaier, F., Stoffel-Wagner, B., 2000. Expression of mineralocorticoid and glucocorticoid receptor mRNA in the human hippocampus. *Neurosci. Lett.* 290 (2), 121–124.
- Wingenfeld, K., Kuehl, L.K., Janke, K., Hinkelmann, K., Dziobek, I., Fleischer, J., Otte, C., Roepke, S., 2014. Enhanced emotional empathy after mineralocorticoid receptor stimulation in women with borderline personality disorder and healthy women. *Neuropsychopharmacology* 39 (8), 1799–1804.
- Wingenfeld, K., Kuehl, L.K., Janke, K., Hinkelmann, K., Eckert, F.C., Roepke, S., Otte, C., 2015. Effects of mineralocorticoid receptor stimulation via fludrocortisone on memory in women with borderline personality disorder. *Neurobiol. Learn. Mem.* 120, 94–100.

- Wingenfeld, K., Otte, C., 2019. Mineralocorticoid receptor function and cognition in health and disease. *Psychoneuroendocrinology* 105, 25–35.
- Wingenfeld, K., Spitzer, C., Rullkötter, N., Löwe, B., 2010. Borderline personality disorder: hypothalamus pituitary adrenal axis and findings from neuroimaging studies. *Psychoneuroendocrinology* 35 (1), 154–170.
- Wingenfeld, K., Wolf, O.T., 2015. Effects of cortisol on cognition in major depressive disorder, posttraumatic stress disorder and borderline personality disorder-2014 Curt Richter award winner. *Psychoneuroendocrinology* 51, 282–295.
- Yehuda, R., Hoge, C.W., McFarlane, A.C., Vermetten, E., Lanius, R.A., Nievergelt, C.M., Hobfoll, S.E., Koenen, K.C., Neylan, T.C., Hyman, S.E., 2015. Post-traumatic stress disorder. *Nat. Rev. Dis. Primers* 1 (1), 15057.