Psychoneuroendocrinology 100 (2019) 254–263

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

PTSD psychotherapy improves blood pressure but leaves HPA axis feedback sensitivity stable and unaffected: First evidence from a pre-post treatment study

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A B S T R A C T

Although key to development of tailored drugs for augmentation treatment of psychotherapy for posttraumatic stress disorder (PTSD), the biological correlates of PTSD remission are still unknown, probably because pre-post treatment studies searching for them are rare. Not even the feedback sensitivity of the otherwise well-studied hypothalamic-pituitary-adrenal (HPA) axis nor arterial blood pressure (BP), which was previously reported to be elevated in PTSD patients, have so far been analyzed during PTSD treatment.

To narrow this knowledge gap, we first performed an overnight dexamethasone suppression test (DST) in a mixed-sex cohort of 25 patients with severe PTSD vs. 20 non-traumatized healthy controls (nt-HC). In addition to hormones, BP and heart rate (HR) were measured at each of the four assessment points (APs). Second, the same parameters were assessed again in 16 of these patients after 12 sessions of integrative trauma-focused cognitive behavioral therapy (iTF-CBT). In relation to nt-HC, PTSD patients showed a significant elevation in HR and diastolic BP while their systolic BP, DST outcomes and basal serum cortisol levels (BSCL) were not significantly altered. In response to iTF-CBT, PTSD symptoms and dysfunctional stress coping strategies improved significantly in PTSD patients. Most important, also their systolic and diastolic BP levels ameliorated at distinct APs while their DST outcomes and BSCL remained unchanged.

To our knowledge, this is the first pre-post treatment study assessing the stability of the DST outcome and BP levels during PTSD treatment. Our results provide first evidence for a non-involvement of HPA axis feedback sensitivity in PTSD symptom improvement and, furthermore, suggest a possible role for BP-regulating pathways such as the sympathetic nervous system in PTSD remission. Limitations arise from the small sample size, the lack of an untreated patient group and drug treatment of patients.

1. Introduction

Posttraumatic stress disorder (PTSD) causes significant suffering that can be relieved by exposure-based psychotherapy in most, but by far not in all cases (Dunlop et al., 2014). Together with the lack of drugs specifically addressing PTSD symptoms, this shows the need for optimization of the current treatment options for PTSD and hence for enlightenment of its biological underpinnings. Disturbances in the autonomic nervous system (Hendrickson and Raskind, 2016) and the hypothalamic-pituitary-adrenal (HPA) axis (Mehta and Binder, 2012; Zaba et al., 2015) have been repeatedly associated with PTSD. However, the abundant findings on HPA axis function in PTSD are inconsistent (Klaassens et al., 2012; Morris et al., 2012).

One of the meta-analyses on this topic reported that PTSD and adult trauma are not linked to HPA axis alterations (Klaassens et al., 2012) while the other concluded that both PTSD and traumatization *per se* attenuate post-dexamethasone (post-dex) cortisol levels (Morris et al., 2012). Our previous finding of a marked inhomogeneity of HPA axis

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https://doi.org/10.1016/j.psyneuen.2018.10.013
Received 19 November 2017; Received in revised form 15 October 2018; Accepted 15 October 2018

response patterns in female PTSD patients (Zaba et al., 2015) offers a likely explanation for this inconsistency: 56,5% of a cohort of PTSD patients exhibited a blunted HPA axis response in the Trier Social Stress Test (TSST) (non-responder patients) while the HPA axis response of the remaining 43.5% (responder patients) was almost identical to that of non-traumatized healthy controls (nt-HC) (Zaba et al., 2015). Very recently, this has been confirmed by others who found exactly the same proportion of TSST responders and non-responders in a fully independent cohort of PTSD patients (Wichmann et al., 2017). Remarkably, these two TSST response patterns were detected, in varying proportions, also among patients with panic disorder and major depression (MDD) as well as among nt-HC (Wichmann et al., 2017). Accordingly, another study found considerable variations in HPA axis dynamics during a pharmacological stress test, i.e. the dexamethasone suppression test (DST), in a cohort of MDD patients (Grunhaus et al., 1987). These studies and our previous finding of an identical PTSD symptom intensity in patient groups with divergent HPA axis responses (Zaba et al., 2015) suggest that the disease state and thus the *maintenance* of psychiatric disorders is most likely independent from HPA axis reactivity, although it currently cannot be excluded that this may not account for the maintenance of distinct psychopathological symptoms. In contrast, there is evidence that the *vulnerability* for stress-related psychiatric diseases such as PTSD might be linked to an altered sensitivity of the glucocorticoid receptor (GR) (de Quervain et al., 2017), a major regulator of the HPA axis, and therewith possibly to an altered HPA axis reactivity. As we, surprisingly, found only four pre-post treatment studies on the role of the HPA axis in PTSD *remission and recovery* (Bergen-Cico et al., 2014; Rauch et al., 2017; Yehuda et al., 2014, 2013), we set out to explore it. Note that the biological underpinnings of disease vulnerability, maintenance and remission can principally derive from different molecular mechanisms.

In general, longitudinal studies investigating the biological correlates of PTSD symptom improvement are rare. In addition to the just cited HPA axis studies, we found one study reporting that narrative exposure therapy improved PTSD associated DNA strand breaks (Morath et al., 2014), four imaging studies (Cisler et al., 2016b, 2016a; Helpman et al., 2016; Simmons et al., 2013) and an investigation of the association of orthostatic blood pressure (BP) regulation with treatment-gains in PTSD (Hinton et al., 2009). The latter contains, to our knowledge, the first and only prospective assessment of BP stability during PTSD treatment, but, however, did not report absolute BP values. Because of the latter and as findings on BP in PTSD are considerably mixed (Edmondson et al., 2017; Murburg et al., 1995; Paulus et al., 2013), we were motivated to assess BP and heart rate (HR) in the course of our DST experiments. Some, but not all, previous studies reported an elevation in systolic BP, diastolic BP and HR in PTSD patients (Edmondson et al., 2017; Murburg et al., 1995; Paulus et al., 2013) while we found no study that detected a PTSD-associated decrease in any of these cardiac parameters.

Studying the role of the HPA axis in disease remission requires its repeated assessment during successful treatment. Pharmacological stress tests such as the DST are particularly suited for this endeavor as they are not prone to habituation. So far, to the best of our knowledge, there are only three publications on serial DSTs in PTSD. Two of them are case reports each describing a single patient (Heber et al., 2002; Kellner et al., 2002) and in the other PTSD symptom intensity remained stable during the observation interval (Wingenfeld et al., 2007). Thus, to the best of our knowledge, the study presented here is the first pre-post treatment study that assessed the stability of the DST outcome and of BP levels during successful PTSD treatment.

2. Materials and methods

2.1. Study design

A graphical overview of the study cohorts is depicted in Fig. 1A. First, we compared psychopathological parameters, BP, HR, plasma adrenocorticotropin (ACTH) and serum cortisol levels in response to 1.5 mg dexamethasone as well as morning basal serum cortisol levels between 25 female PTSD patients and 20 nt-HC. Second, we compared the same parameters in 16 of these patients between two different time-points of treatment, i.e. pre-treatment vs. mid-treatment.

2.2. Participants

With approval from the Ethics Committee of the Ludwig-Maximilians-University in Munich, Germany, we recruited 25 Caucasian PTSD patients and 20 age-matched (± 5 years) nt-HC. All study participants were somatically healthy and free from illicit drug and pathological alcohol use as determined by clinical exam, assessment of medical history and extensive laboratory investigations AH diagnostics were not performed. Patients were treated and studied at the former Trauma Outpatient Clinic of the Max Planck Institute of Psychiatry, Munich, Germany (then-head: Ulrike Schmidt). We included adult (≥18 years) PTSD patients with a Clinician Administered PTSD Scale (CAPS) score of ≥45 which is equivalent to an at least moderate symptom severity of a full DSM-IV PTSD syndrome. Patients with any type of psychotic disorder were excluded. All patients reported PTSD symptoms as chief complaint. Eight patients (32%) were unmedicated, medication of the remaining 68% is explained in the results chapter. All patients were assessed at the start of integrative trauma-focused cognitive behavioral therapy (iTF-CBT) (Schmidt and Gall-Kleebach, 2010) and 16 of them were assessed a second time, i.e. after 12 weekly sessions of therapy. nt-HC were recruited by local advertisements and were free from trauma history, lifetime psychopathology and, except from contraceptives, also from medication. nt-HC were assessed only once. Inclusion and exclusion criteria are described in further detail in Supplemental Table 1.

2.3. 0900 h baseline assessments on the day of participant recruitment

After written informed consent and a 30 min rest, a baseline blood sample was taken at 0900 h in the morning for determination of basal cortisol levels and routine laboratory analyses. Afterwards, demographic and baseline clinical data were assessed: in both patients and nt-HC, DSM-IV current and past psychiatric disorders and traumatic events were evaluated with the Munich Composite Clinical Interview (M-CIDI), depressive symptoms with the German version of the Beck Depression Inventory (BDI), trait and state anxiety with the German version of the State-Trait Anxiety Inventory (STAI), general dissociative symptoms with the German short version of the Dissociative Experience Scale (DES) and positive and negative coping styles with the German version of the Stress Coping Questionnaire (SVF-78). In addition, in PTSD patients, PTSD diagnosis was established with the German version of the DSM-IV CAPS as explained above. Moreover, trauma-related rumination, avoidance (thought suppression) and dissociation were assessed with the Response to Intrusions Questionnaire (RIQ) which was extended with 6 items of the Rumination questionnaire as published by Ehlers 1999. Psychological instruments not cited here are referenced in the Supplemental References chapter.

2.4. Dexamethasone suppression test (DST)

A maximum of two weeks after baseline assessments, a low dose overnight DST was performed in PTSD patients and nt-HC on two consecutive days (d1, d2). The DST assesses the feedback sensitivity of the HPA axis; a decrease in post-dex cortisol levels reflects an increase in post-dex cortisol suppression and therewith an increase in HPA axis reactivity to glucocorticoids (GC). Here, we adapted the DST study protocol by Menke et al. (2012). A graphical overview of the DST is depicted in Fig. 1B. On d1 at 1800 h and 2030 h and on d2 at 1500 h and 1630 h, blood samples were collected via a small catheter placed in

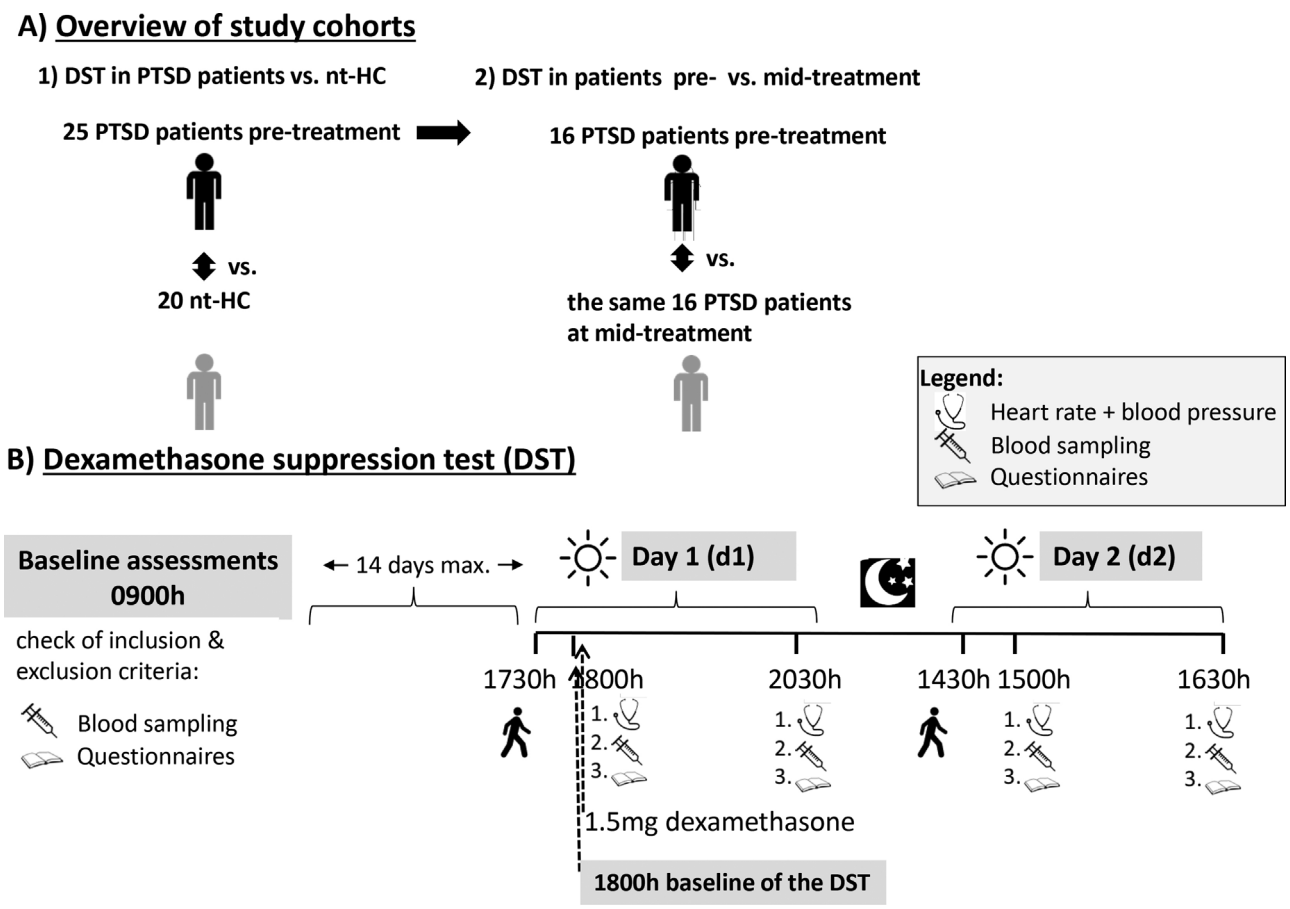

Fig. 1. Graphical overview of (A) study cohorts and (B) experimental set-up of the dexamethasone suppression tests. For further explanations, see main text. Abbreviations: PTSD, posttraumatic stress disorder; DST, dexamethasone suppression test; vs., versus.

a forearm vein. Each blood sampling was preceded by assessment of HR and BP and followed by self-rating questionnaires assessing mood state (Befindlichkeitsskala (BF-S)) and acute dissociative symptoms (Dissociation-Tension-Scale-acute (DSS-acute)) – references for these instruments can be found in the Supplemental References chapter. 1.5 mg dexamethasone was given orally as a tablet immediately after the first blood sampling at 1800 h on d1. Before HR and BP assessment and each blood sampling, participants rested in seated position for at least 30 min. Between 1800 h and 2030 h on d1 and between 1500 h and 1630 h on d2, subjects remained seated in the test room reading magazines or using their laptops. Between the last blood sampling on d1 and the first on d2 participants stayed at home overnight.

2.5. Follow-up assessments of PTSD patients

After 12 weekly sessions of iTF-CBT, 16 out of the 25 PTSD patients were followed up as follows: another baseline blood sample was taken at 0900 h in the morning for re-assessment of basal cortisol levels and routine laboratory parameters. In addition, except for the M-CIDI, all psychometric parameters assessed at baseline were evaluated again at mid-treatment. Finally, a maximum than two weeks after these follow-up assessments, the low dose overnight DST was repeated as described above. In all study patients, PTSD treatment was continued after the end of the study.

2.6. Hormone assays

Concentrations of plasma ACTH and of serum cortisol were quantified with electrochemiluminescence immunoassays (ECLIA) which were performed with the modular analytics EVO analyzer (Roche, Mannheim, Germany). The detection limit of ACTH was 1.0 pg/ml (intra-assay variability < 1%, inter-assay variability ≤3.5%) while that of cortisol was .0018 µg/l (intra-assay variability < 2%, inter-assay variability < 3%).

2.7. HR and BP measurements

HR as well as systolic and diastolic BP were assessed automatically and in parallel using the hand wrist device Boso Medistar® (Bosch & Sohn, Jungingen, Germany). All study participants rested in seated position for at least 30 min before assessment of cardiac parameters.

2.8. Statistical analyses

Group differences in PTSD patients vs. nt-HC were calculated with an unpaired *t*-test (Fig. 2A), or, when appropriate with two-way ANOVA with repeated measures (RM ANOVA) (Figs. 2B–G and 3B–G), with a two-tailed Chi-square test (Tables 1 and 2) or a paired *t*-test (Table 2, Fig. 3A). In case data were not normally distributed, log transformations of cortisol and ACTH raw data were performed. When assumptions of sphericity were violated, Greenhouse–Geisser corrections were conducted. Outliers were identified with the Grubbs test. The number of outliers is reported in the figure legends. All graphs display the results after exclusion of outliers unless no outliers were detected. Statistical details of significant main effects and significant results of between-group Bonferroni post-hoc tests (briefly: post-tests) are either reported in the main text or the respective figure legend. To promote intelligibility, we do not report the statistical details of the extensive amount of significant results of the within-group post- tests but instead highlight only the most important of them in the main text. All data are

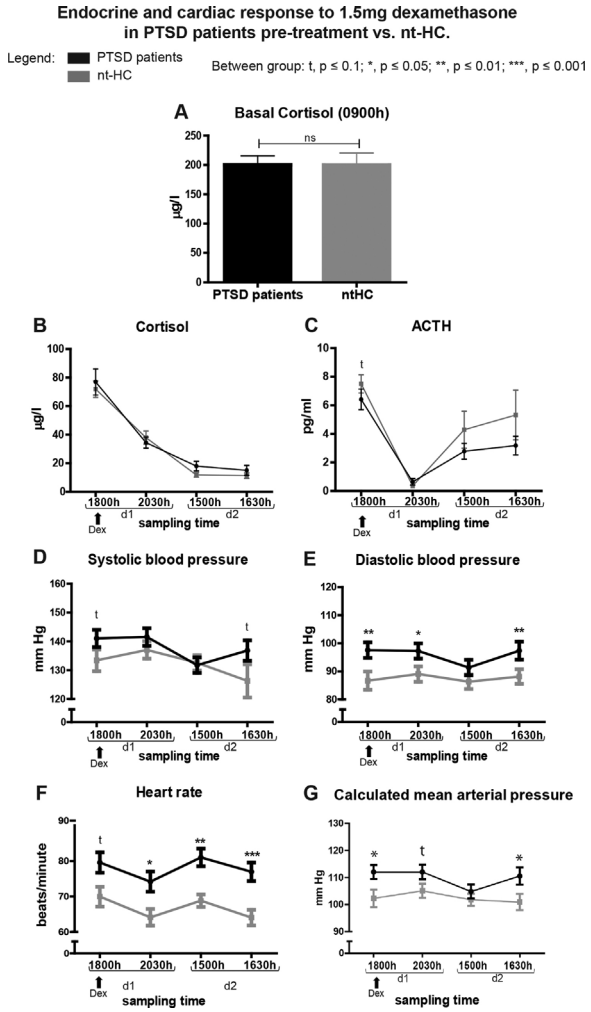

Fig. 2. Endocrine and cardiac response to 1.5 mg dexamethasone in PTSD patients pre-treatment vs. nt-HC. In 25 PTSD patients at the start of therapy vs. 20 nt-HC we compared (A) basal serum cortisol levels at 0900 h as well as (B) serum cortisol levels and (C) plasma adrenocorticotropin (ACTH) levels; (D and E) blood pressure, (F) heart rate and (G) mean arterial pressure (MAP) during a dexamethasone suppression test (DST). The DST protocol is illustrated in detail in Fig. 1 and explained in the methods chapter. Group differences in basal cortisol levels (A) were calculated with an unpaired *t*-test. Group differences in all parameters assessed during the DST (B–G) were calculated with separate two-way ANOVAs with repeated measures (RM ANOVAs) with smoking status as a covariate. RM ANOVAs were followed by Bonferroni corrections (post-hoc tests). Number of outliers excluded: (A) one nt-HC; (B) two patients, two nt-HC; (C) two patients, one nt-HC; (D and E) one nt-HC each; (F) one patient. Missing values: (A) three patients; (B) one patient, one nt-HC; (C) one patient, five nt-HC; (D and E) one patient; (F) one patient. Significant main effects for Group and Time and interactions are reported in the results chapter. Statistical details of significant and trendwise significant results of between-group post-hoc tests: (C) 1800 h: $p = .053$; (D) 1800 h: $p = .090$, 1630 h: $p = .076$; (E) 1800 h: $p = .004$, 2030 h: $p = .013$, 1630 h: $p = .005$; (F) 1800 h: $p = .086$, 2030 h: $p = .032$, 1500 h: $p = .002$, 1630 h: $p = .001$. Symbols: Between group: t, $p \leq .1$; *, $p \leq .05$; **, $p \leq .01$; ***, $p \leq .001$; for reasons of intelligibility, significant within-group effects are not shown. Abbreviations: nt-HC, non-traumatized healthy controls; PTSD, posttraumatic stress disorder; Dex, oral intake of 1.5 mg dexamethasone ; ANOVA, analysis of variance; ACTH, adrenocorticotropic hormone; d, day; vs., versus.

presented as mean ± SEM.

3. Results

3.1. Demographic, clinical and psychological characteristics of the PTSD/HC cohort

We compared 25 PTSD patients (Table 1, 84% females) to 20 nt-HC (Table 1, 80% females). The details of the demographic, clinical and psychological characteristics of the PTSD/HC cohort are shown in Table 1 and summarized briefly in the following: The total last week and last month CAPS scores indicate a severe intensity of the PTSD syndrome in the patient cohort. Accordingly, the results of the DES questionnaire revealed marked elevation in general dissociative symptoms. 18 out of 25 patients (72%) experienced a traumatic event before the age of 18 (early life trauma, ELT) and 18 patients (72%) had suffered traumatizing sexual or both sexual and non-sexual incidents. 15 patients (60%) suffered from a comorbid depressive syndrome, 16 (64%) of a comorbid anxiety disorder. Accordingly, they reported significantly more depressive and anxiety symptoms than nt-HC in the BDI and the STAI, respectively, with the latter pointing at an elevation in both state and trait anxiety. These comorbidity rates fit previous findings in literature. Importantly, PTSD symptoms were the chief complaint in all study patients. As both cohorts differed significantly in their smoking status, we included it as a covariate in all PTSD vs. nt-HC analyses. In contrast, patients and nt-HC did not differ in the distribution of ovarian cycle phases among female individuals. Except from five female nt-HCs with hormonal contraception, all nt-HC were unmedicated. In contrast, only eight patients (32%) received no medication. The majority of patients was already medicated at the start of PTSD treatment. Three of the patients took antidepressants, two of them antipsychotics, another two non-psychotropic drugs and eleven a drug combination. Interestingly, in accordance with our previous findings in another cohort of PTSD patients (Zaba et al., 2015), also PTSD patients studied here used markedly more negative coping strategies and less total positive and type 1 positive coping strategies than nt-HC. Positive coping strategies type 1 comprise minimization and denial of guilt and negative coping strategies comprise self-accusation, rumination, flight and resignation.

3.2. The cortisol and ACTH responses to 1.5 mg dexamethasone did not differ between PTSD patients and nt-HC

First, we assessed HPA axis function in PTSD patients at the start of therapy vs. nt-HC. In accordance with our previous findings in another sample of PTSD patients (Zaba et al., 2015), we found no differences in 0900 h baseline serum cortisol levels between PTSD patients and nt-HC (Fig. 2A, $p = .943$). The functionality of the DST is shown by the marked post-dex negative peak in ACTH levels in combination with the post-dex suppression of cortisol that persisted till the end of the experiment (Fig. 2B and C). Accordingly, main effects for the within-factor Time were significant (Fig. 2B, cortisol: $p = .001$; Fig. 2C, ACTH: $p = .001$). In contrast, we found no significant main effects for Group in the RM ANOVA of log-transformed cortisol and ACTH values and, accordingly, no significant results of the between-group Bonferroni post-tests. Thus, PTSD patients and nt-HC did not differ significantly in their cortisol and the ACTH responses to 1.5 mg dexamethasone. However, there was a statistical trend towards significance for a slight reduction in 1800 h baseline ACTH levels in PTSD patients (Fig. 2C, $p = .53$). For both cortisol and ACTH levels, main effects for the covariate "Smoking status" and for the interaction Time × Group were not significant while the interaction "Time of blood sampling" × "Smoking status" was significant for ACTH (Fig. 2C, $p = .003$), but not for cortisol blood concentrations (Fig. 2B). According to the here-employed protocol of Menke and colleagues (Menke et al., 2012), the dexamethasone suppression status is defined by cortisol levels below 50 ng/ml at 1500 h on

Table 1
Baseline clinical and demographic characteristics of patients with posttraumatic stress disorder (PTSD) and non-traumatized healthy controls (nt-HC).

	PTSD patients (n = 25) M ± SD	nt-HC (n = 20) M ± SD	F value/χ^2
Age (years)	36.72 ± 10.69	36.10 ± 11.93	.03 [1]
Sex (female/male)	21/4	16/4	.12 [2]
BMI	24.91 ± 6.19	23.21 ± 3.96	.29 [1]
Smoking status (yes/no)	13/12	4/16	**4.84*** [2]
Medication (no except from contraceptives/antidepressants/antipsychotics/other/combination)	8/3/1/2/11	20/0/0/0/0	**21.86***** [2]
Ovarian cycle (male/hormonal contraceptives/follicular/ovulation/luteal/menopause/data missing)	4/9/4/1/2/4/1	4/5/4/1/3/2/1	1.45 [2]
Trauma type (I/II)	6/19	–	–
Early life trauma (yes/no)	18/7	–	–
Sexual trauma (yes/no)	18/7	–	–
PTSD severity (total CAPS score) (last week/last month)	75.44 ± 16.99/ 76.48 ± 16.36	–	–
CAPS subscales:			
Re-experiencing (last week/last month)	25.32 ± 6.64/ 26.64 ± 5.82	–	–
Avoidance (last week/last month)	29.36 ± 9.50/ 29.52 ± 8.76	–	–
Hyperarousal (last week/last month)	20.76 ± 6.91/ 20.32 ± 6.91	–	–
Number of comorbid psychiatric disorders	2.48 ± 2.31	–	–
Number of lifetime psychiatric disorders	3.68 ± 2.85	–	–
Comorbid major depression (current/past/no)	15/3/7	–	–
Comorbid anxiety disorders (current/past/no)	16/1/8	–	–
Comorbid substance disorders (current/past/no)	0/8/17	–	–
RIQ subscales:			
Rumination	2.48 ± .67	–	–
Avoidance	2.39 ± .49	–	–
Dissociation	1.98 ± .61	–	–
Dissociation (DES)	24.17 ± 17.83	2.22 ± 3.89	**26.11***** [1]
Depressive symptoms (BDI)	25.25 ± 10.89	1.80 ± 2.44	**88.75***** [1]
Anxiety State (STAI)	57.14 ± 12.54	29.89 ± 5.16	**74.07***** [1]
Anxiety Trait (STAI)	54.90 ± 9.31	29.00 ± 4.60	**115.05***** [1]
Stress coping (SVF-78) subscales:			
Positive coping strategies 1	8.30 ± 3.26	10.68 ± 2.82	**6.64*** [1]
Positive coping strategies 2	10.04 ± 3.57	11.45 ± 3.56	1.74 [1]
Positive coping strategies 3	14.29 ± 4.23	15.63 ± 3.92	1.15 [1]
Positive coping strategies (total)	11.37 ± 2.65	13.04 ± 2.48	**4.53*** [1]
Negative coping strategies	15.12 ± 4.36	8.53 ± 3.48	**30.31***** [1]

Group differences were calculated with: [1], one-way ANOVA (results of Fisher test are shown), or [2], Chi-squared test (χ^2 values are shown). Traumatic events as well as comorbid and lifetime psychiatric disorders were assessed with the Munich Composite International Diagnostic Interview for DSM-IV (M-CIDI). Significant results are marked in bold. For explanation and references of questionnaires and inventories see main text. Abbreviations: M, mean; SD, standard deviation; BMI, body-mass-index; CAPS, Clinician Administered PTSD Scale; RIQ, Response to Intrusions Questionnaire; DES, Dissociative Experiences Scale; BDI, Beck Depression Inventory; STAI, State-Trait Anxiety Inventory; SVF-78, Stress Coping Questionnaire.

* $p \leq .05$.

*** $p \leq .001$.

d2. Using this definition, only one of our patients and two nt-HC were non-suppressors; this small number did not allow for characterization of these two HPA axis feedback sensitivity types.

Furthermore, as expected, the intake of dexamethasone did not lead to a significant change in mood state or acute dissociative symptoms; accordingly, there were no significant main effects for Time (Supplemental Fig. 1A and B). In contrast, main effects for Group were significant. In relation to nt-HC, PTSD patients exhibited a worse mood and significantly more acute dissociative symptoms during the DST (Supplemental Fig. 1A and B; mood: Group: $p < .001$; dissociation: Group: $p < .001$). Taken together, we found that the cortisol and ACTH response to 1.5 mg dexamethasone did not differ in PTSD patients vs. nt-HC. Furthermore, our analyses revealed no evidence for a significant influence of dexamethasone on mood state or acute dissociative symptoms.

3.3. Blood pressure and heart rate were elevated in PTSD patients vs. nt-HC

Next, we compared BP and HR between PTSD patients and nt-HC during the DST. Note that the first assessment point of the DST represents the baseline resting condition at 1800 h. As several previous studies convincingly demonstrated the non-involvement of the HPA axis in BP regulation (Phoon et al., 1997), and as we, accordingly, found BP levels to remain stable in both groups 150 min after oral intake of dexamethasone (Fig. 2D and E, 2030 h) which is known to peak approximately 120 min after its intake, we refrained from studying BP in dexamethasone-untreated control groups. We found a dip in BP levels between 2030 h on d1 and 1500 h on d2 (Fig. 2D and E) that presumably represents the mid-afternoon nadir of the physiological circadian BP rhythm. This BP dip might possibly account for significant main effect of Time in systolic BP (Fig. 2D, $p = .024$), although it did not reach the level of statistical significance in nt-HC but only in PTSD patients who showed a significant decrease in systolic BP between 2030 h and 1500 h (Fig. 2D, $p = .001$) and a significant increase in diastolic BP between the last two assessment points (Fig. 2E, $p = .36$). Also, there was a significant main effect for Time in HR which showed oscillations during the observation interval in both PTSD patients and nt-HC (Fig. 2F, $p = .009$). For none of these three cardiac parameters, the interaction term Time × Group was significant.

Both at 1800 h baseline and at the last assessment point, systolic BP was elevated in PTSD patients over nt-HC at least with a trend towards significance and, accordingly, there was also a trend towards a

Table 2
Baseline clinical and demographic characteristics of patients with posttraumatic stress disorder (PTSD) before and after 12 weekly sessions of PTSD treatment.

	Pre-treatment (n = 16) M ± SD	Mid-treatment (n = 16) M ± SD	T value/χ^2
Age (years)	36.06 ± 11.43		–
Sex (female/male)	12/4		–
BMI	26.71 ± 6.83	26.38 ± 6.87	.87 [1]
Smoking status (yes/no)	5/11		–
Medication (no/antidepressants/antipsychotics/other/combination)	6/2/1/1/6	6/4/0/1/5	2.04 [2]
Ovarian cycle (male/hormonal contraceptives/follicular/ovulation/luteal/menopause/data missing)	4/6/1/1/1/2/1	4/4/3/1/0/2/2	2.37 [2]
PTSD severity (total CAPS score) (last week/last month)	72.06 ± 17.29/ 72.94 ± 16.59	53.94 ± 30.12 55.00 ± 29.84	**2.66*** [1]/ **2.57*** [1]
CAPS subscales:			
Re-experiencing (last week/last month)	24.25 ± 7.21/ 25.50 ± 6.38	18.63 ± 12.94 19.38 ± 12.57	**1.83**t [1]/ **2.11**t [1]
Avoidance (last week/last month)	27.94 ± 10.43/ 28.19 ± 9.39	21.63 ± 11.56 21.63 ± 11.56	**1.85**t [1]/ **2.03**t [1]
Hyperarousal (last week/last month)	19.88 ± 6.58/ 19.25 ± 6.53	13.69 ± 9.69/ 14.00 ± 9.61	**2.53*** [1]/ **2.19*** [1]
Depressive symptoms (BDI)	23.20 ± 10.40	19.31 ± 12.53	**1.97**t [1]
RIQ subscales:			
Rumination	2.37 ± .71	2.05 ± .68	**2.06**t [1]
Avoidance	2.28 ± .51	2.01 ± .65	**2.20*** [1]
Dissociation	1.85 ± .67	1.77 ± .73	.53 [1]
Stress coping (SVF-78) subscales:			
Positive coping strategies 1	8.56 ± 3.74	8.56 ± 3.78	< .001 [1]
Positive coping strategies 2	10.25 ± 3.72	10.97 ± 4.29	−.82 [1]
Positive coping strategies 3	13.57 ± 4.37	13.43 ± 2.45	.17 [1]
Positive coping strategies (total)	11.24 ± 2.91	11.56 ± 2.01	−.44 [1]
Negative coping strategies	14.77 ± 4.62	12.98 ± 5.34	**2.66*** [1]

Group differences were calculated with: [1], paired two-sample t-test, or [2], Chi-squared test (shown are χ^2 values). Significant or trendwise significant results are marked in bold. For explanation and references of questionnaires and inventories see main text. Abbreviations: M, mean; SD, standard deviation; BMI, body-mass-index; CAPS, Clinician Administered PTSD Scale; RIQ, Response to Intrusions Questionnaire; BDI, Beck Depression Inventory; SVF-78, Stress Coping Questionnaire.
[t] $p \leq .1$.
[*] $p \leq .05$.

significant main effect for Group (Fig. 2D, p = .083). Diastolic BP levels were significantly higher in PTSD patients than in nt-HC except for the third assessment point and, consequently, there was a significant main effect for Group (Fig. 2E, p = .002). Accordingly, the mean arterial pressure (MAP) (calculated according to Wilhelm, 2013) was elevated in PTSD patients vs. nt-HC at 1800 h baseline and at the last assessment point of the DST; however, there were no significant main effects for Group and Time (Fig. 2G). Furthermore, also HR was constantly elevated in PTSD patients over nt-HC, both at 1800 h baseline (Fig. 2F, 1800 h) and in response to dexamethasone (Fig. 2F), with a main effect for Group (Fig. 2F, p = .006). HR levels did not meet the cut-off criterion for tachycardia (≥100 beats per minute) at any assessment point. Interestingly, the analysis of diastolic BP (Fig. 2E, p = .036) but not systolic BP or HR analyses (Fig. 2D and F) revealed a significant main effect for "Smoking status". In summary, HR and BP were elevated in PTSD patients vs. nt-HC, however, our analyses are not sufficient to diagnose or exclude AH.

3.4. iTF-CBT successfully improved PTSD symptoms and dysfunctional coping strategies

In the second part of the study, we re-assessed the DST including cardiac parameters after 12 sessions of iTF-CPT. We followed up 16 out of the 25 PTSD patients tested at the start of treatment. First, we re-assessed clinical and psychopathological parameters and compared them to those assessed a pre-treatment. Details of this comparison are shown in Table 2 and summarized in the following: BMI as well as distribution of ovarian cycle phases and medication categories did not change significantly between pre- and mid-treatment. In detail, antipsychotics were discontinued in two patients and switched to antidepressant monotherapy. In the remaining 14 patients, the medication remained unchanged. Most important, PTSD treatment proved to be effective as the mean total CAPS score was significantly reduced from pre- to mid-treatment, namely from a CAPS score of 72.06 pre-treatment to a CAPS score of 53.94 mid-treatment (25.007%) (Table 2). Both the results of the CAPS interview and of the RIQ questionnaire showed an improvement in trauma-associated avoidance anxiety which was significant in case of the RIQ and showed at least a trend towards significance in the CAPS. Furthermore, the CAPS interview revealed a trend towards a significant amelioration in re-experiencing symptoms and a significant improvement in nervous hyperarousal. Furthermore, depressive symptoms improved in response to treatment, at least with a trend towards significance (Table 2) while the acute mood state during the DST remained unaltered (Supplemental Fig. 1C). Interestingly, both acute dissociative symptoms during the DST (Supplemental Fig. 1D) and RIQ-assessed dissociative symptoms (Table 2) did not improve in response to treatment. Accordingly, comparison of the expression of pre-treatment vs. mid-treatment mood and dissociation states with RM ANOVA revealed no significant main effects for Group, respectively, and, accordingly, also no significant results of between-group post-tests (Supplemental Fig. 1C and D). Interestingly, PTSD patients employed significantly less negative (i.e. dysfunctional) coping strategies at mid-treatment than at pre-treatment while the relative underemployment of positive coping strategies type 1 (Table 1) could not be improved (Table 2). As, unfortunately, only few patients returned the FDS and STAI questionnaires, we had to exclude these two instruments from follow-up evaluation. In summary, 12 sessions of iTF-CBT induced a partial remission in the PTSD syndrome which was accompanied by an improvement in dysfunctional coping strategies but not by amelioration in dissociative symptoms.

3.5. PTSD treatment improved elevated BP but left HPA axis feedback sensitivity stable and unaffected

Next, we compared pre- vs. mid-treatment DST outcomes and 0900 h baseline serum cortisol levels. The latter remained stable in response to PTSD treatment (Fig. 3A and B, 1800 h). Most interestingly, the comparison of pre-treatment and mid-treatment concentrations of log-transformed serum cortisol and plasma ACTH levels with RM ANOVA revealed no significant main effects for Group and no significant results of between-group post-tests (Fig. 3B and C). Thus, neither the cortisol nor the ACTH response to dexamethasone changed in response to PTSD treatment. Moreover, the interactions of Group and Time were not significant, either (Fig. 3B and C).

Finally, we analyzed the systolic and diastolic BP in the course of PTSD treatment. Notably, in contrast to HPA axis feedback sensitivity, pathologically elevated BP levels improved after psychotherapeutic treatment: during the DST, we found a significant reduction in systolic BP in two of the four assessment points (Fig. 3D) and in diastolic BP at the last assessment point (Fig. 3E) while HR improved only marginally with a trend towards a significant reduction at 1500 h on day 2 (Fig. 3F). Accordingly, we found significant main effects for Group in the RM ANOVA of systolic BP (Fig. 3D, p = .039) and of diastolic BP (Fig. 3E, p = .011) but not in the RM ANOVA of HR (Fig. 3F). Moreover,

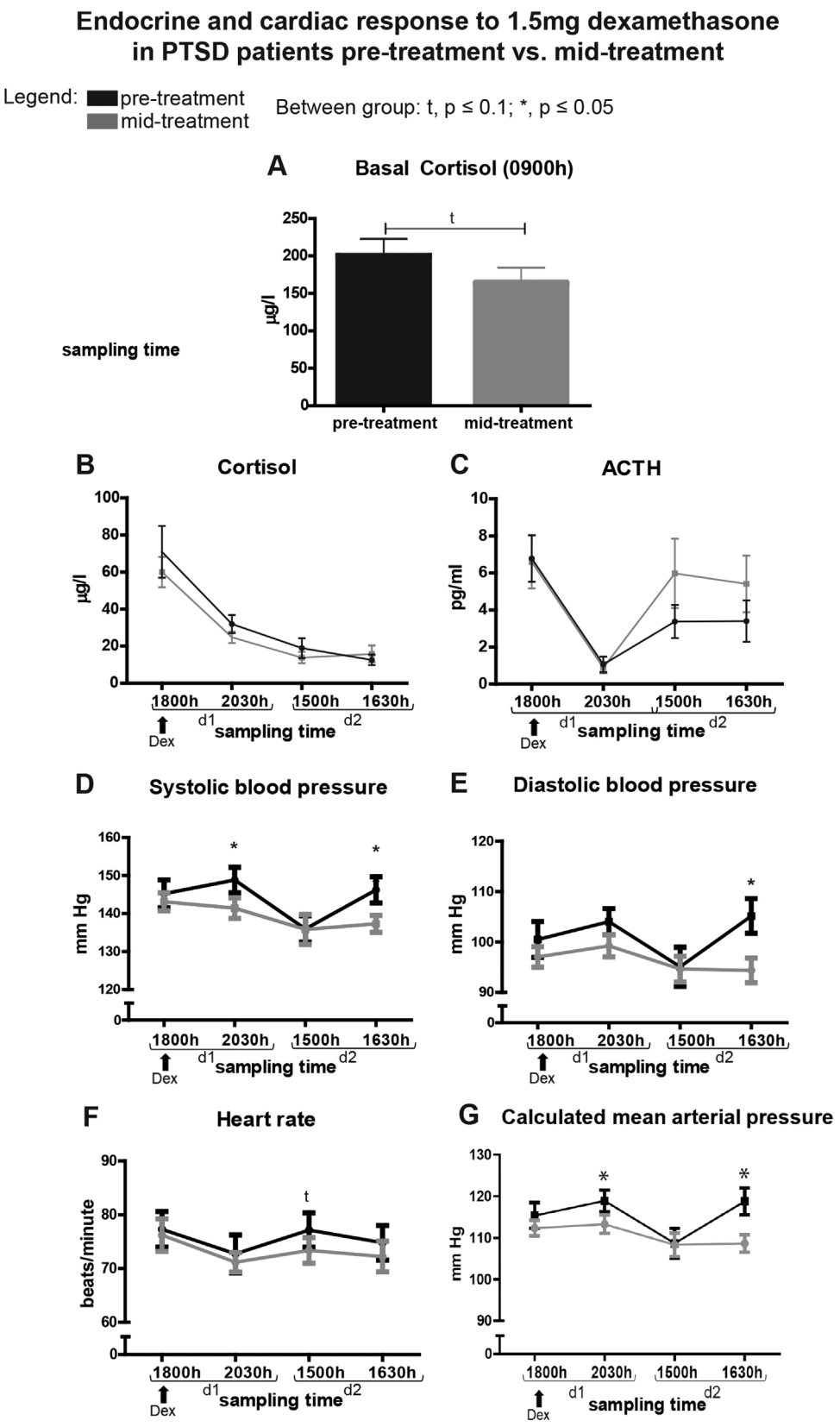

Fig. 3. Endocrine and cardiac response to 1.5 mg dexamethasone in PTSD patients pre-treatment vs. mid-treatment. In 16 patients at the start of treatment vs. mid-treatment (follow-up analysis) we compared (A) basal serum cortisol levels at 0900 h as well as (B) serum cortisol levels and (C) plasma adrenocorticotropin (ACTH) levels; (D and E) blood pressure, (F) heart rate and (G) mean arterial pressure (MAP) during a dexamethasone suppression test (DST). The DST protocol is illustrated in detail in Fig. 1 and explained in the methods chapter. Group differences in basal cortisol levels (A) were calculated with a paired *t*-test. Group differences in all parameters assessed during the DST (B–G) were calculated with separate two-way ANOVAs with repeated measures (RM ANOVAs). RM ANOVAs were followed by Bonferroni corrections (post-hoc tests). Number of outliers excluded: (A) none; (B) three; (C) three; (D and E) none; (F) one. Participants excluded due to missing values: (A) four; (B) one; (C) two; (D and E) one; (F) one. Significant main effects for Group and Time and interactions are reported in the results chapter. Statistical details of significant and trendwise significant results of between-group post-hoc tests: (D) 2030 h: $p = .019$, 1630: $p = .018$; (E) 1630 h: $p = .026$; (F) 1500 h: $t = .079$. Symbols: Between group: t, $p \leq .1$; *, $p \leq .05$; for reasons of intelligibility, significant within-group effects are not shown. Abbreviations: nt-HC, non-traumatized healthy controls; PTSD, posttraumatic stress disorder; DST, dexamethasone suppression test; DEX, oral intake of 1.5 mg dexamethasone; ANOVA, analysis of variance; ACTH, adrenocorticotropic hormone; d, day; vs., versus.

we found that also the calculated MAP decreased significantly in response to psychotherapeutic treatment at two of the four assessment points with significant main effects for Group and Time (Fig. 3G).

Remarkably, 60% of PTSD patients analyzed here suffered of comorbid MDD (Table 1), a psychiatric disorder which has been repeatedly shown to be associated with alterations in HPA axis reactivity (e.g. Juruena et al., 2017). However, adding comorbid depression as a covariate (Fig. 3B–G) did not significantly alter our results. Also, distinct drugs might influence HPA axis reactivity, although literature findings on this topic are mixed (e.g. Künzel et al., 2003; Schüle,

2007). However, as drug treatment was changed in two of the 16 patients only, we refrained from adding drug treatment as a covariate to our pre-post analyses.

4. Discussion

To the best of our knowledge, this is the first prospective study that assessed DST outcomes and absolute BP values in the course of PTSD therapy. We found that successful treatment of PTSD (Table 2) improved dysfunctional cognitive coping strategies (Table 2) and blood pressure (Fig. 3D and E) but left feedback sensitivity of the HPA axis (Fig. 3B and C) and basal cortisol serum levels (Fig. 3A and B) stable and unaffected. These findings are limited by the drug treatment of patients, lack of an untreated patient cohort and the relatively small sample size. Our results of an undisturbed HPA axis response to 1.5 mg dexamethasone in PTSD patients (Fig. 2B and C) are contrary to one (Morris et al., 2012) but in accordance with another meta-analysis on this topic (Klaassens et al., 2012) as well as with the most recent study on DST outcomes in PTSD patients (Michopoulos et al., 2017). Before we became aware of the latter manuscript, we had speculated that reducing the dexamethasone dosage might possibly precipitate between-group differences in HPA axis dynamics. Notably Michopoulos et al. (2017) have now rejected this hypothesis by showing that the exposure of PTSD patients to a considerably lower dosage of dexamethasone (0.5 mg) did not alter their DST response in relation to HC, either – however, that HC cohort consisted of traumatized subjects while we studied nt-HC. Instead, the time-point of traumatization and the sex of study subjects might possibly contribute to the inconsistency of DST results in PTSD as most, although not all, authors proposed them to play a decisive role in HPA axis reactivity modulation (Carpenter et al., 2017; Frodl and O'Keane, 2013; Sandner and Kratzsch, 2017). As we currently cannot clarify the contribution of these important variables to our findings, we plan to assess them systematically in a future study.

The PTSD treatment-gain associated change in GR sensitivity observed previously by others (Yehuda et al., 2014) is *not* inconsistent with the treatment-gain independence of DST outcomes observed here (Fig. 3B and C) since it was assessed in cultured blood cells with the lysozyme inhibition test which specifically measures the sensitivity of the GR (Panarelli et al., 1994) while the *in vivo* DST used here does not (van Leeuwen et al., 2010) due to the often overlooked affinity of dexamethasone for the mineralocorticoid receptor (MR) (van Leeuwen et al., 2010) that modulates HPA axis activity in concert with GR (Harris et al., 2013). Thus, the treatment-gain associated alterations in GR sensitivity in veterans with PTSD (Yehuda et al., 2014) were either compensated or absent in our predominantly female PTSD patient cohort (Fig. 3B and C).

In accordance with our previous findings from an independent PTSD patient sample (Zaba et al., 2015), we found that basal cortisol levels were almost identical in PTSD patients and nt-HC (Fig. 2A) and, moreover, did not change upon PTSD symptom improvement (Fig. 3A). A previous pre-post treatment study reporting that two different treatment procedures differentially influenced salivary diurnal cortisol profiles in veterans with PTSD (Bergen-Cico et al., 2014) and another study showing that a low response to prolonged exposure therapy was associated with an elevated daily cortisol output (Rauch et al., 2017), recall the fact that the analyses employed here are not covering every facet of HPA axis function. However, our findings at least support the hypothesis that both basal activity (Fig. 3A and B) and feedback sensitivity (Fig. 3B and C) of the HPA axis might not be implicated in PTSD symptom improvement. In line with these results, a study that assessed the effects of the GR blocker mifepristone on memory reconsolidation in PTSD patients (Wood et al., 2015) and a randomized controlled trial (RCT) that analyzed the therapeutic effects of hydrocortisone in female PTSD patients (Ludäscher et al., 2015) both dampened the hope for an (additive) therapeutic effect of GC in PTSD which was raised in the same year by another RCT performed in warfighters with PTSD (Yehuda et al., 2015). However, further studies on this topic are needed as these and related previous studies were limited by relatively small sample sizes and as their inhomogeneous study designs complicate their meta-analytic evaluation. Finally, the fact that not all psychopathological symptoms improved in response to treatment, e.g. dissociative symptoms (Table 2 and Supplemental Fig. 1), demonstrates that a role for HPA feedback sensitivity in remission of non-core PTSD symptoms can currently not be excluded. Trials on the efficacy of GC in the secondary prevention of PTSD revealed more homogeneous and promising results which suggest that particularly the prolonged administration of GC might be effective in reducing PTSD risk after trauma exposure (de Quervain et al., 2017).

Notably, the HPA axis responder types that we (Zaba et al., 2015) and others (Wichmann et al., 2017) detected among female PTSD patients in the TSST did not emerge in the DST (Fig. 2B and C) as only 4% (one out of 25) of our study patients were dexamethasone non-suppressors (Fig. 2B and C). This discrepancy most likely results from the different actions of these two stressors: If at all, low dose dexamethasone only poorly crosses the blood brain barrier (BBB) and does not cause a significant psychological stress response (Supplemental Fig. 1) while psychological stressors such as the TSST are designed to elicit stress responses both at the psychological and at the hormonal level. Integration of this knowledge with the synopsis of our TSST (Zaba et al., 2015) and our DST results (Fig. 2B and C; Fig. 3B and C) leads to the assumption that the TSST responder types in female PTSD patients are most likely *not* produced by systemic, i.e. whole body, alterations in molecular HPA axis regulators, but instead by HPA axis regulating mechanisms located in the central nervous system. This is also supported by twin studies showing that heredity appeared to be play a minor role both in the TSST response (Kirschbaum et al., 1992) and in the social stress response of young children, at least in case of high family adversity (Ouellet-Morin et al., 2008).

In contrast to the feedback sensitivity of the HPA axis, BP levels improved considerably in response to successful PTSD treatment (Fig. 3D,E and G) while the tendency for a treatment-induced improvement in elevated HR did not reach statistical significance (Fig. 3F). However, together with the marked elevation in HR in PTSD patients over nt-HC (Fig. 2F), the latter suggests that the impact of PTSD symptom improvement on HR deserves further study.

The facts that during each of the two DSTs all three cardiac parameters undulate and do not constantly decline, that HR but not BP levels were previously shown to habituate across repetitions of stressful speech tasks (Elfering and Grebner, 2012) and that we found no significant differences in pre- vs. mid-treatment psychological stress symptom- and HR level kinetics (Supplemental Fig. 1C and D and Fig. 3F) speak against a habituation bias toward cardiac improvement. As none of the patients was on antihypertensive or antiarrhythmic medication during the assessment period, during which drug treatment was changed anyway only in two of the patients of the pre-post sample (Table 2), we conclude that BP improvement most likely results from the successful psychotherapeutic treatment of PTSD, possibly in particular from improvement in dysfunctional coping strategies (Table 2) which have previously been shown to be more pronounced in TF-CBT responders vs. non-responders (Dondanville et al., 2016). Literature on cardiovascular reactivity to GC is relatively sparse; some authors did not find a major influence of the HPA axis on BP regulation (e.g. Phoon et al., 1997) while others found long-term application of hydrocortisone to increase BP (Werumeus Buning et al., 2016) suggesting that cardiovascular GC reactivity might depend on the dose, time-point and duration of GC application. However, the experiments presented here were not intended for and hence do not allow a conclusion on the influence of dexamethasone on cardiovascular reactivity, mainly as we did not control for circadian BP rhythmicity.

To the best of our knowledge, this is the first prospective pre-post study assessing SVF-78 stress coping strategies and absolute BP levels in PTSD patients during PTSD treatment. Our results on BP are in

accordance with those of a retrospective study that suggested PTSD treatment to reduce the AH risk in PTSD (Burg et al., 2017). Taking into account that the sympathetic nervous system (SNS) is well known for regulating the cardiovascular system (Philipp et al., 1978) and was repeatedly reported to be overactive in PTSD (e.g. Burg et al., 2017), we hypothesize that the here-observed improvement in BP in response to PTSD treatment (Fig. 3D,F and G) might probably result from an attenuation in SNS activity. Accordingly, we postulate that SNS overactivity in PTSD patients might account for the increased in BP in relation to nt-HC (Fig. 2D,F and G).

In conclusion, our results favor a role for the SNS but not for the HPA axis in PTSD symptom improvement and furthermore highlight the risk for BP elevation and therewith for AH in PTSD which should not be overlooked due to its fatal long-term consequences. This inference is in line with studies convincingly demonstrating the efficacy of alpha-adrenoblockers in PTSD treatment (Hendrickson and Raskind, 2016) as well as with numerous studies linking SNS hyperactivity to PTSD (Pitman et al., 2012). Notably, one of the latter detected a peripheral catecholamine hyperdrive in traumatized vs. non-traumatized police officers in response to psychological stress (Otte et al., 2005) thereby motivating us to assess catecholamine levels in PTSD patients in a future TSST study. Integration of the here-reported results (Fig. 3) with the disappointing outcomes of trials that tested the therapeutic efficacy of HPA axis modulation in PTSD (e.g. (Ludäscher et al., 2015; Wood et al., 2015) and the, in contrast, promising effects of adrenoceptor antagonist treatment in PTSD (Hendrickson and Raskind, 2016), strongly suggests that for future studies engaging in the development of the urgently needed drug treatment options for PTSD, modulation of SNS activity might be a more promising endeavor than modulation of the HPA axis.

Funding

Parts of the consumables were funded by the Private Horst Kübler Foundation, Bad Ragaz, Switzerland. The Horst Kübler Foundation had no role in study design, evaluation of results or decision to publish.

Contributions of authors

C.F.S. treated the majority of patients, performed all CIDI interviews, the majority of clinical DST experiments and the majority of CAPS interviews, prepared the database for calculations, calculated all results and prepared all figures and tables except from Fig. 2G and Fig. 3G; M.S. prepared and calculated results of the latter two graphs and supervised all statistical analyses and calculated the results of Fig. 2G and 3G; T.K. performed several DST experiments, draw the majority of DST blood samples and acquired BP and HR raw data; B.W. and D.R.B. draw blood samples and acquired some of the BP and HR raw data; D.J.G. treated several study patients and performed several CAPS interviews; M.U. performed ECLIA analyses; R.R. contributed to the design of the DST experiments, in particular to the selection of psychological instruments and U.S. conceptualized and designed the study, supervised all clinical and molecular experiments as well as the treatment of study patients, performed all medical assessments and blood drawings for 0900 h baseline assessments, prepared blood samples for molecular analyses and wrote the paper. All authors critically revised and approved the version to be published.

Conflicts of interest

C.F.S., M.S., D.J.G., B.W., R.R. and U.S. declare no conflict of interest or financial disclosures related to this work. T.K. is employed at HNMC Brain Health, Munich, Germany. This company had no role in the study design, calculation or interpretation of results or the decision to publish.

Acknowledgement

We thank the Private Horst Kübler Foundation for constant and generous funding of our studies.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.psyneuen.2018.10.013.

References

Bergen-Cico, D., Possemato, K., Pigeon, W., 2014. Reductions in cortisol associated with primary care brief mindfulness program for veterans with PTSD. Med. Care 52, S25–S31. https://doi.org/10.1097/MLR.0000000000000224.

Burg, M.M., Brandt, C., Buta, E., Schwartz, J., Bathulapalli, H., Dziura, J., Edmondson, D.E., Haskell, S., 2017. Risk for incident hypertension associated with posttraumatic stress disorder in military veterans and the effect of posttraumatic stress disorder treatment. Psychosom. Med. 79, 181–188. https://doi.org/10.1097/PSY.0000000000000376.

Carpenter, T., Grecian, S.M., Reynolds, R.M., 2017. Sex differences in early-life programming of the hypothalamic–pituitary–adrenal axis in humans suggest increased vulnerability in females: a systematic review. J. Dev. Orig. Health Dis. 8, 244–255. https://doi.org/10.1017/S204017441600074X.

Cisler, J.M., Sigel, B.A., Kramer, T.L., Smitherman, S., Vanderzee, K., Pemberton, J., Kilts, C.D., 2016a. Modes of large-scale brain network organization during threat processing and posttraumatic stress disorder symptom reduction during TF-CBT among adolescent girls. PLoS One 11, e0159620. https://doi.org/10.1371/journal.pone.0159620.

Cisler, J.M., Sigel, B.A., Steele, J.S., Smitherman, S., Vanderzee, K., Pemberton, J., Kramer, T.L., Kilts, C.D., 2016b. Changes in functional connectivity of the amygdala during cognitive reappraisal predict symptom reduction during trauma-focused cognitive–behavioral therapy among adolescent girls with post-traumatic stress disorder. Psychol. Med. 46, 3013–3023. https://doi.org/10.1017/S0033291716001847.

de Quervain, D., Schwabe, L., Roozendaal, B., 2017. Stress, glucocorticoids and memory: implications for treating fear-related disorders. Nat. Rev. Neurosci. 18, 7–19. https://doi.org/10.1038/nrn.2016.155.

Dondanville, K.A., Blankenship, A.E., Molino, A., Resick, P.A., Wachen, J.S., Mintz, J., Yarvis, J.S., Litz, B.T., Borah, E.V., Roache, J.D., 2016. Qualitative examination of cognitive change during PTSD treatment for active duty service members. Behav. Res. Ther. 79, 1–6.

Dunlop, B., Kaye, J., Youngner, C., Rothbaum, B., 2014. Assessing treatment-resistant posttraumatic stress disorder: the Emory Treatment Resistance Interview for PTSD (E-TRIP). Behav. Sci. 4, 511–527. https://doi.org/10.3390/bs4040511.

Edmondson, D., Sumner, J.A., Kronish, I.M., Burg, M.M., Oyesiku, L., Schwartz, J.E., 2017. The association of PTSD with clinic and ambulatory blood pressure in healthy adults. Psychosom. Med. 1. https://doi.org/10.1097/PSY.0000000000000523.

Elfering, A., Grebner, S., 2012. Getting used to academic public speaking: global self-esteem predicts habituation in blood pressure response to repeated thesis presentations. Appl. Psychophysiol. Biofeedback 37, 109–120. https://doi.org/10.1007/s10484-012-9184-3.

Frodl, T., O'Keane, V., 2013. How does the brain deal with cumulative stress? A review with focus on developmental stress, HPA axis function and hippocampal structure in humans. Neurobiol. Dis. 52, 24–37. https://doi.org/10.1016/j.nbd.2012.03.012.

Grunhaus, L., Flegel, P., Haskett, R.F., Greden, J.F., 1987. Serial dexamethasone suppression tests in simultaneous panic and depressive disorders. Biol. Psychiatry 22, 332–338.

Harris, A.P., Holmes, M.C., de Kloet, E.R., Chapman, K.E., Seckl, J.R., 2013. Mineralocorticoid and glucocorticoid receptor balance in control of HPA axis and behaviour. Psychoneuroendocrinology 38, 648–658. https://doi.org/10.1016/j.psyneuen.2012.08.007.

Heber, R., Kellner, M., Yehuda, R., 2002. Salivary cortisol levels and the cortisol response to dexamethasone before and after EMDR: a case report. J. Clin. Psychol. 58, 1521–1530. https://doi.org/10.1002/jclp.10102.

Helpman, L., Marin, M.-F., Papini, S., Zhu, X., Sullivan, G.M., Schneier, F., Neria, M., Shvil, E., Malaga Aragon, M.J., Markowitz, J.C., Lindquist, M.A., Wager, T., Milad, M., Neria, Y., 2016. Neural changes in extinction recall following prolonged exposure treatment for PTSD: a longitudinal fMRI study. NeuroImage Clin. 12, 715–723. https://doi.org/10.1016/j.nicl.2016.10.007.

Hendrickson, R.C., Raskind, M.A., 2016. Noradrenergic dysregulation in the pathophysiology of PTSD. Exp. Neurol. 284, 181–195. https://doi.org/10.1016/j.expneurol.2016.05.014.

Hinton, D.E., Hofmann, S.G., Pollack, M.H., Otto, M.W., 2009. Mechanisms of efficacy of CBT for Cambodian refugees with PTSD: improvement in emotion regulation and orthostatic blood pressure response. CNS Neurosci. Ther. 15, 255–263. https://doi.org/10.1111/j.1755-5949.2009.00100.x.

Juruena, M.F., Bocharova, M., Agustini, B., Young, A.H., 2017. Atypical depression and non-atypical depression: is HPA axis function a biomarker? A systematic review. J. Affect. Disord. https://doi.org/10.1016/j.jad.2017.09.052.

Kellner, M., Yehuda, R., Arlt, J., Wiedemann, K., 2002. Longitudinal course of salivary cortisol in post-traumatic stress disorder. Acta Psychiatr. Scand. 105, 153–155 discussion 155–156.

Kirschbaum, C., Wüst, S., Faig, H.G., Hellhammer, D.H., 1992. Heritability of cortisol responses to human corticotropin-releasing hormone, ergometry, and psychological stress in humans. J. Clin. Endocrinol. Metab. 75, 1526–1530. https://doi.org/10.1210/jcem.75.6.1464659.

Klaassens, E.R., Giltay, E.J., Cuijpers, P., van Veen, T., Zitman, F.G., 2012. Adulthood trauma and HPA-axis functioning in healthy subjects and PTSD patients: a meta-analysis. Psychoneuroendocrinology 37, 317–331. https://doi.org/10.1016/j.psyneuen.2011.07.003.

Künzel, H.E., Binder, E.B., Nickel, T., Ising, M., Fuchs, B., Majer, M., Pfennig, A., Ernst, G., Kern, N., Schmid, D.A., Uhr, M., Holsboer, F., Modell, S., 2003. Pharmacological and nonpharmacological factors influencing hypothalamic–pituitary–adrenocortical axis reactivity in acutely depressed psychiatric in-patients, measured by the Dex-CRH test. Neuropsychopharmacology 28, 2169–2178. https://doi.org/10.1038/sj.npp.1300280.

Ludäscher, P., Schmahl, C., Feldmann, R.E., Kleindienst, N., Schneider, M., Bohus, M., 2015. No evidence for differential dose effects of hydrocortisone on intrusive memories in female patients with complex post-traumatic stress disorder—a randomized, double-blind, placebo-controlled, crossover study. J. Psychopharmacol. Oxf. Engl. 29, 1077–1084. https://doi.org/10.1177/0269881115592339.

Mehta, D., Binder, E.B., 2012. Gene × environment vulnerability factors for PTSD: the HPA-axis. Neuropharmacology 62, 654–662. https://doi.org/10.1016/j.neuropharm.2011.03.009.

Menke, A., Arloth, J., Pütz, B., Weber, P., Klengel, T., Mehta, D., Gonik, M., Rex-Haffner, M., Rubel, J., Uhr, M., Lucae, S., Deussing, J.M., Müller-Myhsok, B., Holsboer, F., Binder, E.B., 2012. Dexamethasone stimulated gene expression in peripheral blood is a sensitive marker for glucocorticoid receptor resistance in depressed patients. Neuropsychopharmacology 37, 1455–1464. https://doi.org/10.1038/npp.2011.331.

Michopoulos, V., Norrholm, S.D., Stevens, J.S., Glover, E.M., Rothbaum, B.O., Gillespie, C.F., Schwartz, A.C., Ressler, K.J., Jovanovic, T., 2017. Dexamethasone facilitates fear extinction and safety discrimination in PTSD: a placebo-controlled, double-blind study. Psychoneuroendocrinology 83, 65–71. https://doi.org/10.1016/j.psyneuen.2017.05.023.

Morath, J., Moreno-Villanueva, M., Hamuni, G., Kolassa, S., Ruf-Leuschner, M., Schauer, M., Elbert, T., Bürkle, A., Kolassa, I.-T., 2014. Effects of psychotherapy on DNA strand break accumulation originating from traumatic stress. Psychother. Psychosom. 83, 289–297. https://doi.org/10.1159/000362739.

Morris, M.C., Compas, B.E., Garber, J., 2012. Relations among posttraumatic stress disorder, comorbid major depression, and HPA function: a systematic review and meta-analysis. Clin. Psychol. Rev. 32, 301–315. https://doi.org/10.1016/j.cpr.2012.02.002.

Murburg, M.M., McFall, M.E., Lewis, N., Veith, R.C., 1995. Plasma norepinephrine kinetics in patients with posttraumatic stress disorder. Biol. Psychiatry 38, 819–825. https://doi.org/10.1016/0006-3223(95)00044-5.

Otte, C., Neylan, T.C., Pole, N., Metzler, T., Best, S., Henn-Haase, C., Yehuda, R., Marmar, C.R., 2005. Association between childhood trauma and catecholamine response to psychological stress in police academy recruits. Biol. Psychiatry 57, 27–32. https://doi.org/10.1016/j.biopsych.2004.10.009.

Ouellet-Morin, I., Boivin, M., Dionne, G., Lupien, S.J., Arsenault, L., Barr, R.G., Pérusse, D., Tremblay, R.E., 2008. Variations in heritability of cortisol reactivity to stress as a function of early familial adversity among 19-month-old twins. Arch. Gen. Psychiatry 65, 211. https://doi.org/10.1001/archgenpsychiatry.2007.27.

Panarelli, M., Holloway, C.D., Mulatero, P., Fraser, R., Kenyon, C.J., 1994. Inhibition of lysozyme synthesis by dexamethasone in human mononuclear leukocytes: an index of glucocorticoid sensitivity. J. Clin. Endocrinol. Metab. 78, 872–877. https://doi.org/10.1210/jcem.78.4.8157714.

Paulus, E.J., Argo, T.R., Egge, J.A., 2013. The impact of posttraumatic stress disorder on blood pressure and heart rate in a veteran population. J. Trauma. Stress 26, 169–172. https://doi.org/10.1002/jts.21785.

Philipp, T., Distler, A., Cordes, U., 1978. Sympathetic nervous system and blood-pressure control in essential hypertension. Lancet 312, 959–963. https://doi.org/10.1016/S0140-6736(78)92526-6.

Phoon, R.K.S., Tam, S.H., Brown, M.A., Whitworth, J.A., 1997. The role of the hypothalamic-pituitary-adrenal (HPA) axis in the regulation of blood pressure. Clin. Exp. Hypertens. 19, 417–430.

Pitman, R.K., Rasmusson, A.M., Koenen, K.C., Shin, L.M., Orr, S.P., Gilbertson, M.W., Milad, M.R., Liberzon, I., 2012. Biological studies of post-traumatic stress disorder. Nat. Rev. Neurosci. 13, 769–787. https://doi.org/10.1038/nrn3339.

Rauch, S.A.M., King, A.P., Liberzon, I., Sripada, R.K., 2017. Changes in salivary cortisol during psychotherapy for posttraumatic stress disorder: a pilot study in 30 veterans. J. Clin. Psychiatry 78, 599–603. https://doi.org/10.4088/JCP.15m10596.

Sandner, B., Kratzsch, J., 2017. Influence of sex, body mass index and age on the results of the 2-mg overnight dexamethasone suppression test. Lab.-J. Lab. Med.

Schmidt, U., Gall-Kleebach, D., 2010. Besonderheiten der Traumapsychotherapie von Soldaten und Kriegsveteran: Ein Erfahrungsbericht. Psychotherapie 15, 317–321.

Schüle, C., 2007. Neuroendocrinological mechanisms of actions of antidepressant drugs. J. Neuroendocrinol. 19, 213–226. https://doi.org/10.1111/j.1365-2826.2006.01516.x.

Simmons, A.N., Norman, S.B., Spadoni, A.D., Strigo, I.A., 2013. Neurosubstrates of remission following prolonged exposure therapy in veterans with posttraumatic stress disorder. Psychother. Psychosom. 82, 382–389. https://doi.org/10.1159/000348867.

van Leeuwen, N., Kumsta, R., Entringer, S., de Kloet, E.R., Zitman, F.G., DeRijk, R.H., Wüst, S., 2010. Functional mineralocorticoid receptor (MR) gene variation influences the cortisol awakening response after dexamethasone. Psychoneuroendocrinology 35, 339–349. https://doi.org/10.1016/j.psyneuen.2009.07.006.

Werumeus Buning, J., van Faassen, M., Brummelman, P., Dullaart, R.P.F., van den Berg, G., van der Klauw, M.M., Kerstens, M., Stegeman, C.A., Muller Kobold, A., Kema, I.P., Wolffenbuttel, B.H.R., van Beek, A.P., 2016. Effects of hydrocortisone on the regulation of blood pressure - results from an RCT. J. Clin. Endocrinol. Metab. 101 (10), 3691–3699 9 p., jc20162216.

Wichmann, S., Kirschbaum, C., Böhme, C., Petrowski, K., 2017. Cortisol stress response in post-traumatic stress disorder, panic disorder, and major depressive disorder patients. Psychoneuroendocrinology 83, 135–141. https://doi.org/10.1016/j.psyneuen.2017.06.005.

Wilhelm, W. (Ed.), 2013. Praxis der Intensivmedizin: konkret, kompakt, interdisziplinär, 2, akt. u. erw. Aufl. Springer Medizin, Berlin.

Wingenfeld, K., Lange, W., Wulff, H., Berea, C., Beblo, T., Saavedra, A.S., Mensebach, C., Driessen, M., 2007. Stability of the dexamethasone suppression test in borderline personality disorder with and without comorbid PTSD: a one-year follow-up study. J. Clin. Psychol. 63, 843–850. https://doi.org/10.1002/jclp.20396.

Wood, N.E., Rosasco, M.L., Suris, A.M., Spring, J.D., Marin, M.-F., Lasko, N.B., Goetz, J.M., Fischer, A.M., Orr, S.P., Pitman, R.K., 2015. Pharmacological blockade of memory reconsolidation in posttraumatic stress disorder: three negative psychophysiological studies. Psychiatry Res. 225, 31–39. https://doi.org/10.1016/j.psychres.2014.09.005.

Yehuda, R., Bierer, L.M., Pratchett, L.C., Lehrner, A., Koch, E.C., Van Manen, J.A., Flory, J.D., Makotkine, I., Hildebrandt, T., 2015. Cortisol augmentation of a psychological treatment for warfighters with posttraumatic stress disorder: randomized trial showing improved treatment retention and outcome. Psychoneuroendocrinology 51, 589–597. https://doi.org/10.1016/j.psyneuen.2014.08.004.

Yehuda, R., Daskalakis, N.P., Desarnaud, F., Makotkine, I., Lehrner, A.L., Koch, E., Flory, J.D., Buxbaum, J.D., Meaney, M.J., Bierer, L.M., 2013. Epigenetic biomarkers as predictors and correlates of symptom improvement following psychotherapy in combat veterans with PTSD. Front. Psychiatry 4. https://doi.org/10.3389/fpsyt.2013.00118.

Yehuda, R., Pratchett, L.C., Elmes, M.W., Lehrner, A., Daskalakis, N.P., Koch, E., Makotkine, I., Flory, J.D., Bierer, L.M., 2014. Glucocorticoid-related predictors and correlates of post-traumatic stress disorder treatment response in combat veterans. Interface Focus 4, 20140048. https://doi.org/10.1098/rsfs.2014.0048.

Zaba, M., Kirmeier, T., Ionescu, I.A., Wollweber, B., Buell, D.R., Gall-Kleebach, D.J., Schubert, C.F., Novak, B., Huber, C., Köhler, K., Holsboer, F., Pütz, B., Müller-Myhsok, B., Höhne, N., Uhr, M., Ising, M., Herrmann, L., Schmidt, U., 2015. Identification and characterization of HPA-axis reactivity endophenotypes in a cohort of female PTSD patients. Psychoneuroendocrinology 55, 102–115. https://doi.org/10.1016/j.psyneuen.2015.02.005.