

Resting-state functional connectivity after hydrocortisone administration in patients with post-traumatic stress disorder and borderline personality disorder



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Abstract

In a previous study, we found that - in contrast to healthy individuals - patients with borderline personality disorder (BPD) and post-traumatic stress disorder (PTSD) showed better memory retrieval performance after hydrocortisone administration compared to placebo. As these results suggest an altered function of corticosteroid receptors in the brain in PTSD and BPD, we examined the effect of hydrocortisone on brain activation in both disorders. We recruited 40 female healthy controls, 20 female unmedicated patients with PTSD and 18 female unmedicated patients with BPD. We conducted a placebo-controlled cross-over study, in which all participants underwent two resting state MRI measurements after they received either a placebo or 10 mg hydrocortisone orally and in randomized order. There was a time interval of one week between the measurements. We analysed resting state functional connectivity (RSFC)

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Amygdala;
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with the hippocampus and the amygdala as seed regions. Compared to healthy controls, both patient groups showed reduced hippocampus RSFC to dorsomedial prefrontal cortex (dmPFC). Positive hippocampus dmPFC RSFC correlated negatively with childhood trauma ($r = -0.47$) and with severity of clinical symptoms, measured with the Borderline Symptom List ($r = -0.44$) and the Posttraumatic Stress Diagnostic Scale ($r = -0.45$). We found neither differences in amygdala RSFC nor an effect of hydrocortisone administration. Childhood trauma might lead to decreased positive hippocampus dmPFC RSFC. This might explain symptoms of PTSD and BPD that are characterized by dysfunctional fear regulation.

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1. Introduction

Stress-related mental disorders such as posttraumatic stress disorders (PTSD) and borderline personality disorder (BPD) have been characterized by altered glucocorticoid sensitivity (Szeszko et al., 2018; Wingenfeld et al., 2010). Heim and colleagues suggested that neuroendocrine changes due to early-life stress may reflect a risk factor for developing psychiatric disorders (Heim et al., 2000; Heim and Nemeroff, 2001, 2008), which has been emphasized for PTSD by Yehuda and colleagues (Yehuda, 2009; Yehuda et al., 2004). Similar results have been described for patients with BPD (Fernando et al., 2012; Simeon et al., 2007). In response to hydrocortisone, a synthetic glucocorticoid, we found that – in contrast to healthy controls – patients with BPD and PTSD had better memory retrieval performance suggesting an altered function of corticosteroid receptors in the brain (Wingenfeld et al., 2012, 2013) and the hypothalamic-pituitary-adrenal (HPA) axis. In PTSD, an enhanced feedback sensitivity of the HPA axis is the most prominent finding, which has been interpreted as enhanced sensitivity of corticosteroid receptors (Rohleder et al., 2004; Yehuda et al., 2004). In BPD patients, results on HPA axis function remain more heterogeneous, but preliminary evidence also suggests an enhanced sensitivity to glucocorticoids (Wingenfeld et al., 2013; Wingenfeld and Wolf, 2015). Altered volumes of hippocampus and amygdala, which are rich of corticosteroid receptors, have additionally been described in PTSD (Logue et al., 2018; Pietrzak et al., 2015) and in BPD (Aguilar-Ortiz et al., 2018; Wingenfeld et al., 2010).

To our knowledge, there is only one study investigating the effect of glucocorticoids on brain activation during rest in patients with PTSD using positron emission tomography (PET). In that study, 17.5 mg of hydrocortisone were administered before [¹⁸F]FDG PET was conducted (Yehuda et al., 2010). Military veterans with PTSD showed no hydrocortisone-associated decrease in hippocampal FDG uptake, whereas veterans without PTSD showed a decrease in hippocampal [¹⁸F]FDG uptake after hydrocortisone administration. No study investigated the effects of hydrocortisone on brain activity in patients with BPD or in individuals who reported childhood trauma.

In healthy individuals, there are some studies on the effects of glucocorticoids and stress on brain activity. One resting state fMRI study, in which 10 mg hydrocortisone was administered, reported decreased activation in the amygdala and hippocampus (Lovallo et al., 2010). Similarly, in response to stress, a network of limbic structures including the hippocampus and amygdala was deactivated (Pruessner et al., 2008). These results underline the important role of

the hippocampus with its high density of corticosteroid receptors (De Kloet et al., 2016) in the regulation of negative feedback of the HPA axis (Wingenfeld and Wolf, 2014).

Resting state functional connectivity (RSFC) can be used to analyse, which brain regions are co-activated and are, thus, functionally related. Stress increased RSFC of the bilateral amygdala with dorsal ACC, anterior insula, and a dorso-rostral pontine region (Van Marle et al., 2010) and hydrocortisone led to bilateral amygdala decoupling by reducing positive functional connectivity (Henckens et al., 2011). In addition, it has been shown that hippocampus RSFC with the left amygdala and right middle temporal gyrus (MTG) increased immediately following stress (Vaisvaser et al., 2013) and that bilateral hippocampus mPFC positive functional coupling is upregulated after stress (Admon et al., 2009).

Alterations in RSFC have been additionally described for patients with PTSD and BPD. Patients with PTSD showed stronger positive functional coupling between the right amygdala and insula (Rabinak et al., 2011) and the left amygdala and the pregenual anterior cingulate cortex (ACC), dorsomedial prefrontal cortex (dmPFC), and the right amygdala and the dorsal ACC (Brown et al., 2014). In addition, decreased positive bilateral posterior hippocampus RSFC with the default-mode network was shown as well (Chen and Etkin, 2013). A review of neuroimaging-based findings in patients with PTSD suggested decreased neuronal integrity of the hippocampus in PTSD and a failed inhibition of amygdala by the medial prefrontal cortex and the hippocampus (Fenster et al., 2018; Shin et al., 2006; Yehuda et al., 2015).

Patients with BPD exhibited increased positive RSFC between the bilateral amygdala and the bilateral (para-) hippocampus and right dmPFC as well as stronger positive dACC connectivity with left insula, posterior cingulate, superior temporal gyrus, and occipital gyrus and right dmPFC (Krause-Utz et al., 2014a). In addition, high resting state activity in the left hippocampus and amygdala, with increased RSFC with the ACC was described in patients with BPD, suggesting that the amygdala is overactive at rest (Salvador et al., 2016). Furthermore, for patients with BPD lower intrinsic functional connectivity in the right hippocampus (Doll et al., 2013) and lower positive mean RSFC in the default mode network, including hippocampus, was shown (Quattrini et al., 2019).

In addition, patients with BPD and PTSD exhibited marked disturbances in fronto-limbic brain circuits at rest and during emotional or cognitive challenging tasks (Krause-Utz et al., 2014b; Minzenberg et al., 2007; Morey et al., 2008). However, so far, no study has investigated the influence of hydrocortisone on RSFC in both disorders in the same study.

Taken together, previous research showed altered corticosteroid receptor sensitivity and alterations in the hippocampus and amygdala functioning in patients with PTSD and BPD. Also, there is evidence for decreased RSFC of the hippocampus and failed inhibition of the amygdala. In addition, hippocampus and amygdala RSFC seem to be influenced by stress. Although there is extensive evidence for lateralized effects in RSFC in BPD and PTSD and the influence of stress on RSFC, these lateralized effects seem not to be overlapping across groups and effects of stress. Therefore, the aim of the current study was twofold: (1) to investigate differences in bilateral hippocampus and bilateral amygdala RSFC, which we expect to be decreased especially to prefrontal areas, in both patients groups in comparison to healthy controls; (2) to examine the effects of hydrocortisone administration on RSFC of the hippocampus and amygdala in an explanatory manner. However, we expect differences in hydrocortisone effects on amygdala and hippocampus RSFC between healthy controls and patients with PTSD and BPD due to altered glucocorticoid sensitivity in the latter groups.

2. Experimental procedures

2.1. Participants

We recruited 40 healthy controls, 20 medication-free patients with PTSD and 18 medication-free patients with BPD. Diagnosis was determined by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, SCID I & II) (Fydrich et al., 1997; Wittchen et al., 1997). Trained clinical psychologists (S.M., J.F.) performed the interviews. The short version of the Borderline Symptom List (BSL-23) was conducted (Bohus et al., 2009). Participants were asked to rate their current symptoms on a 5-step Likert scale (0 = not at all, 4 = very strong). In the second part of the questionnaire, dysfunctional behavior is assessed with 11 items, again on a 5-step Likert scale. Furthermore, the Posttraumatic Stress Diagnostic Scale (PDS-r) (Foa, 1995) was conducted. It includes a trauma checklist and assesses the 17 PTSD symptoms (according to DSM IV). Respondents are asked to rate the severity of the symptom on a 4-step Likert scale from (0 = not at all or only one time) to (3 = 5 or more times a week / almost always). We assessed severity of childhood trauma with the Childhood Trauma Questionnaire (CTQ) (Bernstein and Fink, 1998). Within this questionnaire, 28 items assess five different types of early life stress (ELS): emotional abuse, physical abuse, emotional neglect, physical neglect and sexual abuse. Participants should describe whether these events happened during their childhood on a Likert scale from 1 = never to 5 = very often.

A current episode of major depressive disorder (MDD) as comorbid disorder led to exclusion from the study. Further exclusion criteria were schizophrenia, schizoaffective disorder, bipolar disorder, and anorexia nervosa as current comorbid disorders. CNS diseases or severe somatic diseases, metabolic or endocrine disorders, autoimmune diseases, current infections, pregnancy, a body mass index (BMI) above 30 and intake of any psychotropic medication also led to exclusion for all participants. In addition, healthy controls were excluded if they met diagnostic criteria for past or present diagnosis of any DSM-IV axis I or axis II disorder. A history of psychiatric or psychotherapeutic treatment also led to exclusion in the control group. For all participants, any fMRI contraindication (e.g. pacemaker or non-removable metals) represented additional exclusion criteria. Participants were right-handed and native German speakers.

In- and outpatients were recruited at the Department of Psychiatry and Psychotherapy, Charité Berlin, Campus Benjamin Franklin, Germany. Outpatients and healthy controls were recruited via advertisement and received financial remuneration (100 Euro). Procedures were carried out with the participants' full understanding and written informed consent was obtained prior to participation. The study was approved by the Local Ethics Committee and in accordance with Declaration of Helsinki.

2.2. Procedure

We conducted a placebo-controlled cross-over study, in which all participants underwent two resting state MRI measurements after they received either a placebo or 10 mg hydrocortisone orally and in randomized order, with a time interval of one week between the measurements (days: $M = 20.77$, $SD = 20.39$).

Test sessions started at 3.30 pm in the afternoon. After 45 min of resting period, participants entered the scanner and were instructed to look at a fixation cross and to not think about anything, while resting state fMRI was recorded. We repeated the measurement with at least one-week interval. Throughout the afternoon saliva samples were collected at beginning (+0) and +15 min, +60 min, +120 min and +135 min after the first saliva sample. Saliva samples were collected using Salivette devices (Sarstedt). After collection, which took place at room temperature, saliva samples were stored at -80°C until biochemical analysis. Cortisol concentration was determined in the Neurobiology Laboratory of the Dept. of Psychiatry, Charité University Berlin. Free cortisol was analyzed using a commercially available TR-FRET-based, in-house adopted immunoassay (Cisbio International, Codolet, France), which was performed according to the manufacturer's instructions. Intraassay coefficients of variation were below 8%, interassay coefficients of variation were below 10% (Duesenberg et al., 2016).

2.3. MR imaging acquisition

We collected fMRI resting state data with a 3 Tesla Siemens Magnetom TrioTim (3T) system using a 12-channel radiofrequency head coil. Resting state data were acquired using an echoplanar imaging (EPI) pulse sequence [3.0 mm slices acquired sagittal, repetition time (TR)= 2000 ms, echo time (TE)= 30 ms, flip angle=70°, matrix=64x64, field of view (FOV) = 192 mm, voxel size=3 × 3 × 3 mm³] with 180 EPI images. In addition, we acquired 3D high-resolution T1-weighted anatomical MRI with 176 slices (voxel size=1 × 1 × 1 mm³) for co-registration at the end of each scanning session. Participants were instructed to look at a fixation-cross and to not think about anything. FMRI recording was only started after participant's full understanding and consent and lasted 6 min.

2.4. Data analysis

2.4.1. Salivary cortisol concentration data analysis

We analyzed cortisol values using a repeated measures analysis of variance (rmANOVA) with condition (hydrocortisone vs. placebo) and time (five measurement points) as within-subject factors and group (healthy controls, PTSD, BPD) as between-subject factor. In case of significant results, we carried out post-hoc t-tests. This primarily served as a treatment check for hydrocortisone administration.

2.4.2. MR imaging data analysis

We performed image preprocessing and analyses using DPARSF (DPABI V2.2_161201) and SPM 12 (Wellcome Trust Centre for Neu-

roimaging, UK; <http://www.fil.ion.ucl.ac.uk/spm>) under the version of MathWorks Matlab R2015a. Image preprocessing consisted of reorientation, removal of the first 5 images, slice timing, coregistration, segmentation and nuisance covariates regression. We furthermore excluded subjects with very high maximum motion (above 3 mm) and with a high percentage of micro-movement ($> 50\%$). This resulted in the exclusion of 1 healthy control, 5 patients with PTSD and 2 patients with BPD due to high movement, leaving 39 healthy controls, 15 patients with PTSD and 16 patients with BPD for final analysis. We filtered the signal (0.01–0.1 Hz), normalized into MNI space, smoothed the signal with a 6 Full Width at Half Maximum (FWHM) Kernel Filter and additionally used scrubbing for time points of extensive movement. Since previous literature has shown effects of hydrocortisone bilaterally on hippocampus and amygdala (Lovallo et al., 2010), and alterations of these regions have been described in patients with BPD and PTSD (Krause-Utz et al., 2014a; Rabinak et al., 2011; Salvador et al., 2016; Shin et al., 2006), we selected the hippocampus and amygdala as a priori regions of interest (ROI). We generated bilateral masks of the hippocampus and amygdala using the probabilistic Harvard-Oxford subcortical structural atlases in FSL. Only voxels that were part of these regions with a probability of at least 50% were included in the mask. Temporal correlation between the mean time series of the hippocampus and amygdala with the time series of every voxel in the brain were calculated. The correlation coefficients of each voxel were normalized to z-scores with Fisher's *r*-to-z transformation. We then carried out a full factorial analysis in SPM 12 using the functional connectivity z-maps with hippocampus and amygdala as seed regions. We were interested in the main effect group, the main effect condition and the interaction group x condition on a whole brain level with Family Wise Error (FWE) cluster correction ($p < 0.025$, using a primary voxel-wise threshold of $p < 0.001$, uncorrected, $k > 50$). Since we were interested in two seeds (bilateral amygdala and bilateral hippocampus), the cluster correction threshold of $p < 0.05$ was Bonferroni-corrected resulting in a threshold of $p < 0.025$. In case of significant results, we performed post-hoc t-tests to identify differences between each pair of groups or conditions on a whole brain level ($p < 0.025$, using a primary voxel-wise threshold of $p < 0.001$, uncorrected, $k > 50$). In addition, we build spherical ROIs of 5 mm around peak voxel obtained in main effect or interaction and extracted mean z values representing RSFC between each pair of ROIs. Magnitude of RSFC within these clusters was extracted and correlated with CTQ (severity of childhood trauma), PDS-r (symptom severity in PTSD), and BSL-23 scores (symptom severity in BPD). Furthermore, correlation analyses were performed between magnitude of RSFC and salivary cortisol levels.

3. Results

3.1. Sample characteristics

The groups did not differ in age, level of education, intake of contraceptives, menstrual cycle phase at both measurements, smoking habits and BMI (all $p > 0.05$). As expected, the three groups differed in clinical measures (PDS-r, BSL-23, CTQ) ($p < 0.001$). Healthy controls scored lower in these questionnaires than patients with PTSD or BPD ($p < 0.001$). No differences in these measures between the patient groups were found ($p > 0.05$) (see Table 1).

According to the SCID I Interview, patients with PTSD reported current comorbid bulimia nervosa $n=2$ and panic disorder $n=3$. Patients with BPD reported the following current axis I disorders: bulimia nervosa $n=2$, PTSD $n=4$, social phobia $n=1$. Patients with BPD described the following lifetime diagnosis: Major depressive episode (MDE)

$n=6$, panic disorder $n=1$, anorexia nervosa $n=1$, bulimia nervosa $n=1$, agoraphobia $n=1$, adjustment disorder $n=1$, alcohol abuse = 3, alcohol dependency = 1, substance abuse = 6. Patients with PTSD described the following lifetime diagnosis: MDE $n=4$, alcohol abuse $n=2$, alcohol dependency $n=1$ and substance abuse $n=1$.

3.2. Effects of hydrocortisone administration on salivary cortisol concentration

We conducted a rmANOVA analyzing salivary cortisol concentration. This primarily served as a treatment check for hydrocortisone administration. One patient with PTSD, one patient with BPD and one healthy control could not be included in the analysis due to missing data at one measurement point. We log-transformed cortisol values to get normally distributed values. We used Greenhouse-Geisser coefficients due to violation of sphericity assumption. Homogeneity of variances between groups could be assumed.

The rmANOVA revealed a significant main effect for time ($F(2.04, 130.27) = 70.42, p < 0.001$) and condition ($F(1,64) = 257.65, p < 0.001$) and a significant condition x time interaction effect ($F(1.88, 120.19) = 216.21, p < 0.001$), indicating an increase in cortisol after hydrocortisone administration. Accordingly, post hoc t-tests revealed significant difference between the placebo condition and the hydrocortisone condition at time points +60 +120 and +135 ($p < .001$) (see Fig. 1).

Furthermore, there was a main effect of group ($F(2, 64) = 4.54, p < 0.05$), and a trend towards an interaction of group with time and condition ($F(3.76, 120.19) = 2.45, p = 0.053$). Post hoc t-test indicated that patients with PTSD had lower cortisol levels than patients with BPD at the first two measurement points in the hydrocortisone condition ($p < 0.01$) and at least on trend level in all measurement points in the placebo condition (all $p < 0.1$).

3.3. Seed-based functional connectivity

3.3.1. Hippocampus

The full factorial analysis of seed-based hippocampus RSFC revealed neither a main effect of condition nor a condition x group interaction. Thus, across groups, hydrocortisone administration did not lead to changes in hippocampus-associated RSFC.

However, there was a significant main effect of group in hippocampus RSFC with the dmPFC ($p < 0.001$), (see Fig. 2). We used post-hoc t-tests to separately compare groups. Analyses revealed that positive hippocampus RSFC with the dmPFC is decreased in both, patients with PTSD ($p < 0.01$) as well as patients with BPD ($p < 0.01$) compared to healthy controls and independent of condition (see Table 2), with no difference between the patient groups.

Since scores of CTQ, PDS-r and BSL-23 were not normally distributed, we used non-parametric Spearmann-correlation to correlate scores with the magnitude of RSFC. We used Bonferroni correction for multiple testing. Hippocampus dmPFC RSFC correlated negatively with CTQ ($r(69) = -0.47, p < 0.001$), PDS-r ($r(60) = -0.46, p < 0.001$) and BSL-23 scores ($r(61) = -0.44, p < 0.001$) in the placebo

Table 1 Sample characteristics.

	HC	PTSD	BPD	Statistics
Age M (\pm SD)	28.65 (\pm 7.27)	29.67 (\pm 9.33)	27.87 (\pm 4.34)	$P = 0.93$
Years of education	12.04 (\pm 1.36)	11.33 (\pm 1.92)	12.06 (\pm 1.44)	$p = 0.31$
Smokers Y/N	10/28	7/8	7/9	$p = 0.26$
BMI ^a	21.91 (\pm 2.44)	22.69 (\pm 3.85)	22.66 (\pm 4.35)	$p = 0.64$
Menstrual cycle				
T1	Luteal	28/9	6/7	$p = 0.13$
T2	Luteal	26/10	10/3	$p = 0.81$
Intake of oral contraceptives		11/27	2/13	$p = 0.44$
BSL-23 ^b		0.10 (\pm 0.10)	1.34 (\pm 0.84)	$P < 0.01$ $BPD = PTSD \setminus HC$
PDS-r ^c		0.26 (\pm 0.86)	29.71 (\pm 13.48)	$P < 0.001$ $BPD = PTSD \setminus HC$
CTQ		30.74 (\pm 5.39)	61.77 (\pm 21.52)	$P < 0.001$ $BPD = PTSD \setminus HC$

HC = healthy controls, PTSD = patients with posttraumatic stress disorder, BPD = patients with borderline personality disorder, BMI = body mass index, T1 = first measurement point, T2 = second measurement point, BSL 23 = short version of the borderline symptom checklist, PDS = posttraumatic stress diagnostic scale, CTQ = childhood trauma questionnaire. Missing data: ^a2 HC, ^b4 Patients with PTSD, 3 Patients with BPD, ^c5 HC, 5 patients with PTSD, 2 patients with BPD.

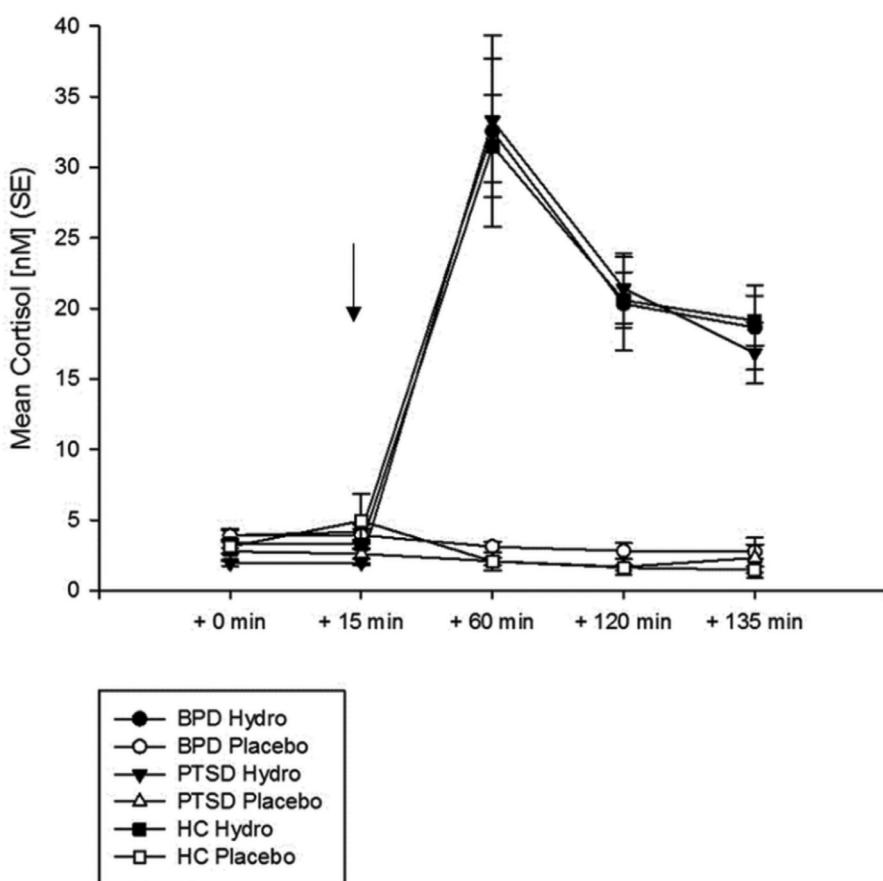


Fig. 1 Salivary cortisol concentrations at beginning (+0) and +15 min, +60 min, +120 min and +135 min after the first saliva sample. The administration of hydrocortisone or placebo was directly after measurement 2 (+15 m) (indicated by the arrow). In the hydrocortisone condition participants showed significant higher salivary cortisol concentrations after drug administration (samples +60, +120, +135 min) in all three groups.

HC = healthy controls, BPD = patients with borderline personality disorder, PTSD = patients with posttraumatic stress disorder.

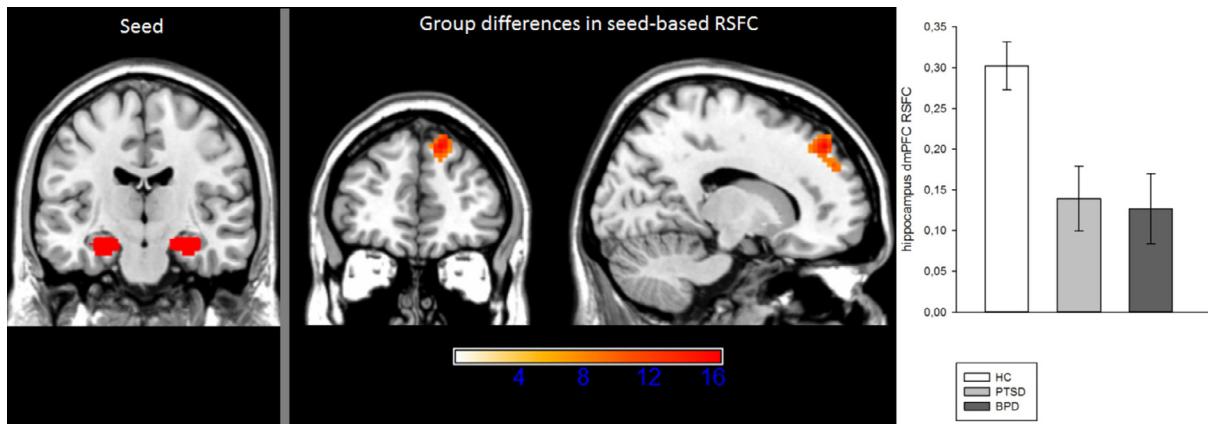


Fig. 2 Main effect group in full factorial analysis. Reduced hippocampus dmPFC resting state functional connectivity in patients with PTSD and patients with BPD compared to healthy controls, with no difference between the patient groups. RSFC = resting state functional connectivity. For depiction the threshold was set to $p < .001$ uncorrected with an extent threshold of $k > 50$ voxels. Values represent F values of main effect.

Table 2 Functional connectivity of the hippocampus.

Region	Contrast	Side	Coordinates	pFWE	Cluster size
dmPFC	HC>PTSD	R	15 45 45 (Z: 4.84)	$p < 0.01$	103
dmPFC	HC>BPD	R	18 45 48 (Z: 4.33)	$p < 0.01$	107

dmPFC = dorsomedial prefrontal cortex, HC = healthy controls, PTSD = patients with posttraumatic stress disorder, BPD = patients with borderline personality disorder. Analyses with Family Wise Error (FWE) cluster correction ($p < 0.025$, using a primary voxel-wise threshold of $p < 0.001$, uncorrected, $k > 50$). R = right, L = left. The values in the table represent z values with peak voxel coordinates in the MNI stereotactic space.

condition and at least on trend level in the hydrocortisone condition (CTQ ($r(68) = -0.46$, $p < 0.001$), PDS-r ($r(60) = -0.41$, $p < 0.01$), BSL ($r(61) = -0.33$, $p = 0.05$) across groups (see Figure 3). In addition, we computed non-parametric partial correlation to control for PTSD and BPD symptoms. Non-parametric partial correlation controlling for PDS-r scores was significant between CTQ and hippocampus dmPFC RSFC in the placebo condition (CTQ ($r(59) = -0.32$, $p < 0.01$), and in the hydrocortisone condition (CTQ ($r(59) = -0.35$, $p < .05$)). Non-parametric partial correlation controlling for BSL-scores revealed a trend in the placebo condition (CTQ ($r(60) = -0.21$, $p = 0.10$), and was significant in the hydrocortisone condition (CTQ ($r(60) = -0.27$, $p < .05$)). After controlling for CTQ scores, none of the other correlation were significant ($p > 0.05$). None of the correlations between magnitude of RSFC and cortisol values were significant ($p > 0.05$).

3.3.2. Amygdala

Full factorial analysis of functional connectivity of the amygdala revealed no main effect of condition or group nor an interaction of group and condition on a whole brain level.

4. Discussion

We investigated resting state functional connectivity (RSFC) of the hippocampus and amygdala in patients with PTSD and BPD in comparison to each other and to healthy con-

trols. We further examined the effects of hydrocortisone administration on RSFC of the hippocampus and amygdala. Both patient groups showed reduced positive RSFC between hippocampus and dmPFC compared to healthy controls independent of condition, with no difference between both patient groups. This was in accordance with our first hypothesis, expecting decreased hippocampus RSFC in both patient groups. Positive hippocampus dmPFC RSFC correlated negatively with severity of childhood trauma and clinical severity of both disorders. We found no effects in amygdala RSFC. Across groups, there were no differences in RSFC between the hydrocortisone and the placebo condition.

The positive hippocampus mPFC functional coupling is susceptible to the influence of stress (Admon et al., 2009). In addition, alterations in this hippocampus mPFC functional coupling were described for many stress-associated mental disorders (Godsil et al., 2013) including PTSD (Jin et al., 2014; Malivoire et al., 2018). Birn and colleagues investigated whether childhood maltreatment, combat exposure, and combat-related posttraumatic stress symptoms predict hippocampus and amygdala RSFC in male veterans (Birn et al., 2014). They reported that childhood trauma and combat exposure negatively predicted RSFC between hippocampus and mPFC, which is in line with our results. Interestingly, Admon and colleagues demonstrated that in healthy controls the hippocampus vmPFC positive functional coupling is upregulated after stress and an increase in stress symptoms is related to a weaker hippocampus vmPFC functional coupling. Thus, an increase in positive hippocampus

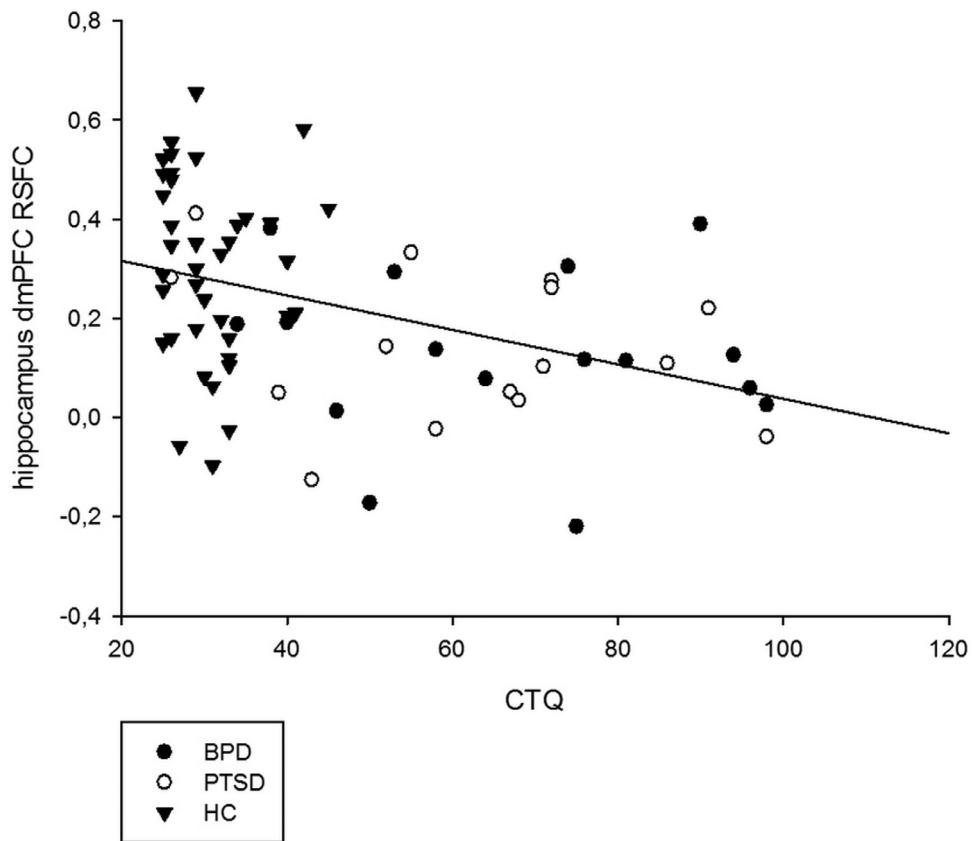


Fig. 3 Correlation between CTQ and hippocampus dmPFC resting state functional connectivity. Amount of hippocampus dmPFC resting state functional connectivity correlated negatively with CTQ scores across all groups, with patients groups having higher CTQ scores than healthy controls.

CTQ = childhood trauma questionnaire, dmPFC = dorsomedial prefrontal cortex, RSFC = resting state functional connectivity, HC = healthy controls, BPD = patients with borderline personality disorder, PTSD = patients with posttraumatic stress disorder.

PFC RSFC might be a possible mechanism for an adaptive reaction to stress by establishing processes needed for extinction (Admon et al., 2009).

In our study, the effect of reduced positive hippocampal RSFC was restricted to the dmPFC. This is in line with previous results, which described in response to threat an inverse pattern of activation between hippocampus and dmPFC, hippocampus deactivation and dmPFC activation (Lissek et al., 2013). In addition, the dmPFC is involved in recognizing and regulating emotions (Kim and Hamann, 2007; Modinos et al., 2010). Again, alterations in dmPFC by traumatic events were shown in former studies: Greater activation in the dmPFC while appraising fearful faces after traumatic events positively correlated with PTSD symptoms after the traumatic event (Wang et al., 2016). In a recently published study (Abdallah et al., 2017), the authors investigated global brain connectivity and seed-based anatomical connectivity of the anterior hippocampus in patients with PTSD. Severity of symptoms correlated negatively with global connectivity and anatomical connectivity of the anterior hippocampus. When investigating dimension specific PFC functional connectivity, the authors found that the dmPFC functional connectivity correlated negatively with arousal.

Since we investigated patients with PTSD and BPD in the same study, we were able to compare both groups. How-

ever, in our sample patient groups did not differ in clinical measures (PDS-r, BSL-23) and childhood experiences (CTQ). Given these circumstances, one might argue that a common causal factor for reduced positive hippocampus dmPFC RSFC might be childhood trauma, as suggested by correlations of hippocampus dmPFC RSFC with CTQ in our study and former research (Birn et al., 2014). Childhood trauma might lead to a decreased positive hippocampus dmPFC RSFC. This might then cause an altered response to threat, for which the hippocampus dmPFC interaction has been shown to be relevant (Lissek et al., 2013). This might in turn partly explain the lack of reduction in fear response, described in PTSD (Norholm and Jovanovic, 2018) and BPD (Kamphausen et al., 2013), resulting in symptoms such as hyperarousal in PTSD (Norholm and Jovanovic, 2018) and emotional dysregulation in BPD (Kamphausen et al., 2013). This model is also supported by previous studies. Birn and colleagues argue that childhood trauma may weaken fear regulation by impairing functional connectivity between the hippocampus and PFC (Birn et al., 2014). Notably, the hippocampus plays an important role in the regulation of fear by limiting fear responses via PFC (Maren et al., 2013). In rats, chronic stress impairs hippocampus-mPFC long-term potentiation, which is central for the regulation of conditioned fear (Garcia et al., 2008). It is possible that childhood trauma com-

promises this ability to upregulate hippocampus PFC RSFC, increasing the risk for developing psychopathology as suggested by Birn et al. (2014).

To our knowledge, so far there is no study describing decreased positive RSFC between hippocampus und dmPFC in patients with BPD. However, our results suggest hippocampus dmPFC functional coupling to be relevant in patients with BPD. Of note, altered hippocampal volume in BPD (Aguilar-Ortiz et al., 2018; Wingenfeld et al., 2010) and disturbances in fronto-limbic brain circuits at rest and during emotional or cognitive challenging tasks (Krause-Utz et al., 2014b) would further support our results.

However, contrary to our first hypothesis, we did not find any differences in amygdala RSFC, which is furthermore not in line with previous research. In patients with PTSD, studies showed stronger functional coupling between the amygdala and insula (Rabinak et al., 2011). Furthermore, increased amygdala activity in response to fearful stimuli and decreased positive amygdala-prefrontal RSFC has been shown in patients with PTSD (Stevens et al., 2013). In addition, patients with BPD showed high resting activity in left hippocampus and amygdala (Salvador et al., 2016). In addition, increased positive RSFC between the bilateral amygdala and the bilateral (para-) hippocampus and right dmPFC (Krause-Utz et al., 2014a) and diminished positive amygdala-prefrontal connectivity after an emotion regulation task in comparison with healthy controls (Baczkowski et al., 2017; Kamphausen et al., 2013) were described in patients with BPD. These results suggest that increased amygdala activation and its decreased positive RSFC to prefrontal regions (Kamphausen et al., 2013; Stevens et al., 2013) is central for the pathology of both disorders. Former studies investigated either amygdala activity or amygdala post task RSFC using fearful stimuli (Kamphausen et al., 2013; Stevens et al., 2013) or an emotion regulation task (Baczkowski et al., 2017) or had larger sample sizes in patient groups (Krause-Utz et al., 2014a; Salvador et al., 2016). The absence of an intervention to create amygdala activation and insufficient sample size might have been contributing factors possibly explaining the absence of amygdala RSFC alterations in our resting state study.

In addition, contrary to our second hypothesis, we did not find any effects of hydrocortisone administration on hippocampus or amygdala RSFC across groups nor a difference in effects of hydrocortisone between groups. There are only few studies investigating glucocorticoid effects on RSFC in healthy participants. Veer and colleagues described higher baseline cortisol in relation to stronger negative RSFC between amygdala and mPFC (Veer et al., 2012), suggesting that the regulation of the amygdala by the mPFC is modulated by cortisol in order to control stress response and emotional reaction. After psychosocial stress induction, the authors described increased RSFC between amygdala and dorsal anterior cingulate cortex, anterior insula, and a dorso-rostral pontine region (Van Marle et al., 2010) and amygdala and the posterior cingulate cortex, precuneus and the mPFC (Veer et al., 2011), whereas hydrocortisone administration led to amygdala decoupling, by reducing positive functional connectivity (Henckens et al., 2011). Of note, Admon and colleagues could demonstrate that hippocampus vmPFC functional connectivity is influenced by stress in healthy controls (Admon et al., 2009). However, previous

studies using hydrocortisone administration preferably used different designs and dosages. With 10 mg, we used a relatively low dose of hydrocortisone in comparison to other studies using up to 100 mg hydrocortisone (Symonds et al., 2012). In addition, previous studies used intravenous injection (Lovallo et al., 2010). Lovallo and colleagues found decreased hippocampus and amygdala activity after 10 mg hydrocortisone i.v. administration (Lovallo et al., 2010). However, in that study, the authors investigated regional BOLD response rather than connectivity and scanned participants over an interval of 40 Min. Furthermore, task-based fMRI studies with hydrocortisone administration (Fleischer et al., 2018; Symonds et al., 2012) investigated different parameters and different activated networks. Reduced prefrontal activation during autobiographical memory retrieval (Fleischer et al., 2018) and decreased activation in limbic structures during cognitive tasks (Lovallo et al., 2010; Pruessner et al., 2008) have been described in response to stress or increased glucocorticoid level. Furthermore, a decreased cerebral blood flow of the parahippocampal gyrus during impaired declarative memory retrieval in response to cortisone, was described (De Quervain et al., 2003). The differences in total number of scans, timing and investigated parameters makes a direct comparison of effects difficult.

4.1. Strengths and limitations

Beside the strength of a relatively large sample, which includes patients with PTSD, BPD and healthy controls with an overall sample size of 70 participants (all patients were unmedicated), several limitations needs to be addressed.

Our sample consisted of women only. Therefore, our results are not transferable to men. Although correlation with CTQ values indicate an influence of traumatic events experienced during childhood, trauma during adulthood was also frequent in both groups and might have influenced the results. In addition, although groups did not differ in menstrual cycle, non-controlling for menstrual cycle phase might have influenced the responses to hydrocortisone and might have covered group differences due to its effects on the HPA axis activity.

Furthermore, given the high BSL scores in the PTSD group, the high PDS-r scores in the BPD group, and the fact that many BPD patients additionally fulfilled PTSD criteria, one might argue that patient groups were not distinct enough to reveal additional differences.

Although current MDD was an exclusion criteria, comorbidities as described above, for example lifetime substance abuse or MDD might have influenced the results. An influence of both disorders on hippocampus RSFC has been described (Kaiser et al., 2015; Ma et al., 2011): Hippocampus mPFC RSFC has shown to positively correlate with depressive symptoms in nondemented elderly (Goveas et al., 2011) and to be decreased in cocaine users (Gu et al., 2010).

As already mentioned above, the dosage of 10 mg hydrocortisone was lower compared to other fMRI studies (Symonds et al., 2012) or different protocols (Lovallo et al., 2010) were used. Nevertheless, with 10 mg the increase in saliva cortisol is larger in comparison to the response in a psychosocial stress paradigm (Pruessner et al., 2008).

In addition, Lovallo and colleagues scanned participants repeatedly over 40 min resulting in a larger number of scans (Lovallo et al., 2010). Therefore, the total number of 180 images in this study might have been insufficient in their power to detect additional effects. In addition, the use of a cluster correction threshold might have increased the chance of false positive results.

Although the sample size in post-hoc t-tests is quite limited, the overall sample size included in the correlation is relatively large in comparison to other studies. Since patient groups were rather small, correlation within each groups would have massively decreased the sample size. However, correlations across groups might be confounded with other explaining variables. Nevertheless partial correlation controlling for PTSD and BPD symptoms hint towards an influence of childhood trauma rather than psychopathology.

Our control of movement artefacts led to a smaller sample size, but increased precision. Sample sizes of patient groups are nevertheless comparable to former studies (Milad et al., 2009). However, the sample size still might have been insufficient to detect additional effects in amygdala RSFC or effects of hydrocortisone.

5. Conclusion

Taken together, we found a reduced positive hippocampus dmPFC RSFC across patient groups. In addition, positive hippocampus dmPFC RSFC correlated negatively with severity of childhood trauma and severity of clinical symptoms. Childhood trauma might cause a decreased positive hippocampus dmPFC RSFC resulting in an altered threat response. Future studies should further investigate how hippocampus dmPFC RSFC is influenced by stress throughout the lifespan to ascertain the causal direction.

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Declaration of Competing Interest

All authors reported no biomedical financial interests or potential conflicts of interest.

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Contributors

All authors have personally reviewed and given final approval of this manuscript.

Katja Wingenfeld, Christian Otte, Stefan Röpke and Oliver Wolf have made substantial contribution to the conception and design of the study. Juliane Fleischer, Moritz Düsenberg and Sabrina Golde have made substantial contribution to the acquisition and analysis of data and Matti Gärtner and Simone Grimm have made substantial contribution to the analysis and interpretation of the data. Sophie Metz made substantial contribution to the analysis and interpretation of the data and writing of the article.

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