Psychoneuroendocrinology (2012) 37, 1048—1056

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Cortisol has enhancing, rather than impairing effects on memory retrieval in PTSD

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Received 16 August 2011; received in revised form 1 December 2011; accepted 1 December 2011

KEYWORDS
PTSD;
Declarative verbal memory;
Autobiographical memory;
Cortisol;
HPA axis

Summary
Background: In the present study, we aimed to compare the effect of exogenous cortisol on memory retrieval in posttraumatic stress disorder (PTSD) with the effects in healthy controls. In healthy participants, administration of cortisol impairs declarative memory retrieval. Only a few studies have investigated these effects in PTSD yielding mixed results.
Methods: In a placebo-controlled crossover study, 44 patients with PTSD and 65 healthy controls received either placebo or 10 mg of hydrocortisone orally before memory testing. In addition to declarative memory retrieval (word list learning), we also tested autobiographical memory retrieval specificity.
Results: In both tasks opposing effects of cortisol on memory were observed when comparing patients with controls. In controls, cortisol had impairing effects on memory retrieval, while in PTSD patients cortisol had enhancing effects on memory retrieval in both memory domains.
Conclusions: The present results suggest beneficial effects of acute cortisol elevations on hippocampal mediated memory processes in PTSD. Possible neurobiological mechanisms underlying these findings are discussed.

1. Introduction

In posttraumatic stress disorder (PTSD), in contrast to major depressive disorder (MDD), reduced basal cortisol levels and enhanced negative feedback of the hypothalamus pituitary adrenal (HPA) axis are prominent findings (Yehuda, 2002). These results have often been interpreted in the context of

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doi:10.1016/j.psyneuen.2011.12.002

enhanced glucocorticoid receptor (GR) sensitivity (Yehuda, 2009; Rohleder et al., 2010). In addition to a more pronounced cortisol suppression even after a low dose of dexamethasone, changes in number and responsiveness of GR have been reported (Yehuda et al., 2004). However, there are also contradictory findings (Pace et al., 2012). A meta-analysis revealed that gender as well as type of trauma plays a role in HPA axis dysregulation in PTSD (Meewisse et al., 2007). Low cortisol has been found predominantly in patients with PTSD due to sexual or physical abuse. Comorbid major depressive disorder might also be relevant (de Kloet et al., 2008).

Neuropsychological alterations are also an important feature in PTSD. Problems particularly with learning and memory have been found, including deficits in verbal declarative memory as well as autobiographical memory, i.e. overgeneralized autobiographical memory retrieval (Buckley et al., 2000; Golier and Yehuda, 2002; Schonfeld and Ehlers, 2006). Patients with overgeneralized memory have difficulties in retrieving specific autobiographical events; instead, they tend to reply with abstract or general memory content (e.g. they summarize several different events).

In healthy humans, most studies suggest impairing effects of glucocorticoids on memory retrieval, especially hippocampus based declarative memory retrieval, while consolidation seem to be improved by glucocorticoids (Wolf, 2003, 2009; Het et al., 2005; de Quervain et al., 2009). Up to now, studies that investigate the effects of cortisol administration or stress exposure on memory in patients with PTSD are rare and yielded inconclusive results (Bremner et al., 2004; Grossman et al., 2006; Yehuda et al., 2007, 2010). However, none of these studies focused on memory retrieval, but instead administered cortisol before memory encoding and thus are unable to separate the effects of cortisol on acquisition, consolidation and retrieval. This might be one reason for the conflicting results. In PTSD, one study reported stronger negative effects of hydrocortisone treatment on declarative memory (Grossman et al., 2006), which is in line with the hypotheses of an enhanced GR sensitivity in patients suffering from PTSD (Vythilingam et al., 2006). In older PTSD patients opposing effects have been reported, namely a more pronounced enhancement of declarative memory performance (Yehuda et al., 2007). However, findings are equivocal (Yehuda et al., 2010). Importantly, sample sizes of these previous studies were rather small thus limiting the conclusions that can be drawn. Furthermore, most participants in these studies were male and two of the three studies investigated war veterans. However, PTSD is more prominent in women and, therefore, it would be of great interest to study also female patients.

Major depression is also characterized by cognitive impairments and HPA axis dysregulations, however in this disorder reduced rather than enhanced GC sensitivity has been observed (Holsboer, 2000; Rohleder et al., 2010) accompanied by HPA hyperactivity. It thus might be of interest to compare the effects of cortisol administration on memory between the two disorders. In a series of studies with patients suffering from major depressive disorder, we investigated the effects of 10 mg hydrocortisone in different memory domains. In line with the literature, hydrocortisone treatment impaired declarative memory retrieval, working memory, and autobiographical memory specificity in healthy controls (Schlosser et al., 2010; Terfehr et al., 2011a,b). In contrast, these impairing effects were not observed in MDD patients. We suggested that the lacking effect of acute cortisol elevations on memory might be due to reduced functioning of hippocampal and/or prefrontal GRs in those patients (Schlosser et al., 2011; Wingenfeld and Wolf, 2011).

In the present study, we aimed to further investigate the effect of exogenous cortisol on declarative and autobiographical memory performance in PTSD. For the first time in PTSD patients, we used a study design which specifically investigates memory retrieval. Based on the results of Grossman (Grossman et al., 2006) and the hypothesis of enhanced GR sensitivity in PTSD (Yehuda et al., 2004, 2006), it could be assumed that hydrocortisone would lead to a stronger memory retrieval impairment in patients with PTSD. However, based on previous studies reporting memory enhancing properties of cortisol in PTSD patients (Yehuda et al., 2007) and initial observations of beneficial effects of cortisol treatment on PTSD symptoms (Aerni et al., 2004), the opposite prediction (enhanced memory retrieval after cortisol administration) appeared equally likely.

2. Methods and materials

2.1. Participants

44 patients with PTSD and 65 healthy controls aged of 18 years or older (range 20—58 years) participated in our study (see Table 1). In the PTSD there were 38 women and six men, while the control groups consisted of 42 women and 23 men. Fifty-one of the control participants were part of a former study by our working group (Terfehr et al., 2011a). Patients were recruited at the Department of Psychiatry and Psychotherapy Bethel (Ev. Hospital Bielefeld, Germany), and at the Department of Psychosomatic Medicine and Psychotherapy, University Medical Center Hamburg-Eppendorf & Schön Klinik Hamburg-Eilbek, Germany.

Participants were excluded if they had any of the following current or previous medical conditions: CNS relevant somatic diseases or severe somatic diseases (e.g. neurological diseases), metabolic diseases (e.g. thyroid disease, diabetes), organic shift in cortisol secretion (e.g. Cushings syndrome), immune-mediated diseases, medicated hypertension, or current infections. Further exclusion criteria were pregnancy, current anorexia, current or lifetime schizophrenia, alcohol or drug dependence, bipolar disorder, schizoaffective disorder, major depression with psychotic symptoms, attention deficit hyperactivity disorder or cognitive impairment. Intake of antidepressants did not lead to exclusion.

Written informed consent was obtained from all participants. Healthy participants were recruited by local advertisement and received financial remuneration for their efforts (100€). The study was approved by the University of Muenster Ethics Committee and the Ethics Committee of the Medical Council of Hamburg.

2.2. Procedure

To assess psychiatric diagnoses participants were interviewed using the Structured Clinical Interview for DSM-IV Axis I and II

Table 1 Experimental protocol indicating time of cognitive testing.

Day	Time	Procedure[a]
Day 1	1530	Word list learning and immediate recall
Day 2	1545	Administration of hydrocortisone or placebo
	1615	Word list (delayed recall)
	1645	Autobiographical memory test

[a] One week later the study protocol was repeated using the alternate condition (hydrocortisone/placebo) and parallel versions of the memory tests.

(First et al., 1997; Wittchen et al., 1997). PTSD symptoms (patients only) were also assessed with the post-traumatic stress diagnostic scale (PDS) (Foa, 1995). Depressive mood state was measured in all participants using the Beck Depression Inventory (BDI) (Beck and Steer, 1994). In order to provide a measure for general mental ability, two subtests (LPS 3 and LPS 4) of a well established German intelligence test, the ''Leistungsprüfsystem'' (LPS) (Horn, 1983) were administered. The LPS is partially based upon Thurstone's (1938) primary mental abilities and correlates highly with other popular psychometric intelligence tests (Horn, 1983).

In this placebo-controlled, double-blind cross-over study, each participant was tested twice with parallel versions of a word list paradigm and an autobiographical memory test (AMT) (see below). All tests took part in the afternoon. The two versions of the tests were counterbalanced across the two test conditions. On the first day all participants learned the word list. On the second day, 30 min after administration of 10 mg hydrocortisone (Jenapharm®) or placebo the participants were asked to recall the words from the word list they had learned the day before (free recall). Furthermore, the AMT was performed. The same procedure with the alternate test condition was repeated after one week. The study protocol is presented in Table 1.

The word list paradigm consisted of 21 words. Participants were asked to memorize as many words as possible in no particular order. Word lists were taken from a study of Kuhlmann et al. (2005) and were reduced from 30 to 21 words (Terfehr et al., 2011a). One reason for reducing the word list was that we were investigating psychiatric in-patients. Our aim was to have a word list learning paradigm which was not too difficult for the patients. A standard neuropsychological test, the Auditory Verbal Learning Test (AVLT) consists of 15 words and is appropriate to investigate patient populations. The two word lists were comparable in valence, word usage, and word length.

A modified version of the AMT (Williams and Broadbent, 1986; Buss et al., 2004; Schlosser et al., 2010) was applied. After an initial practice on one cue word, the participants were instructed to write down a specific event from their past in response to six adjectives which were consecutively presented on cards. Participants were instructed to recall events that had happened at least one day prior to testing, that had taken place at a certain time and place, and did not last any longer than one day. They were also instructed to describe individuals and specific activities involved in the event. The specificity of the answers was evaluated by two trained raters, separately. An answer was considered specific when at least three of the following criteria were met: description of the location, time, and persons involved and activities carried out. Each specific answer was given a score of 1 and non-specific answers a score of 0 (see also, Schlosser et al., 2010).

2.3. Statistical analysis

Statistical analyses were performed using SPSS Version 18.0. Demographic data were analyzed using Pearson's Chi^2-test for categorical data and Student's *t*-test for continuous data.

Effects of hydrocortisone on memory performance were analyzed using analysis of variance (ANOVA) with repeated measurements. Post hoc *t*-tests were performed in case of any significant group by condition interaction effect for each group separately. To control for potential confounders, separate ANCOVAs were performed for continuous variables, e.g. age, BMI and estimated intelligence, while dichotomous variables, such as gender, intake of oral contraceptive, smoking and medication intake were introduced as an additional group factor into the ANOVAs. Additionally, non-parametric statistics were used.

3. Results

3.1. Demographic and clinical data

Demographic and clinical data as well as the related statistics are presented in Table 2. Patients with PTSD and healthy controls were comparable in age and body mass index (BMI) (see Table 1). The PTSD group consisted of more women ($N = 38$, 86.4%) compared to the control group ($N = 42$, 64.6%). In the PTSD group 7 women took oral contraceptives compared to 14 in the control group, which was not a significant difference. There were more smokers in the PTSD group. Concerning estimated intelligence (LPS), we found PTSD patients to have lower scores.

Patients had a significantly higher depression score (BDI). However, PTSD patients with and without comorbid MDD did not differ in terms of BDI scores (see Table 2). We also compared PTSD patients with and without comorbid MDD concerning self-reported PTSD symptoms (PDS). As presented in Table 2 both groups did not differ.

PTSD patients suffered from the following current comorbid diagnosis: major depressive disorder ($N = 23$), anxiety disorder ($N = 8$), pain disorder ($N = 1$), eating disorder ($N = 6$), obsessive—compulsive disorder ($N = 3$), alcohol abuse ($N = 1$). Furthermore, the following personality disorders were diagnosed: paranoid personality disorder $N = 1$, borderline personality disorder $N = 22$, avoidant personality disorder $N = 9$, dependent $N = 2$ personality disorder. The patients took the following psychiatric medications: selective serotonin reuptake inhibitor $N = 10$, selective noradrenergic and serotonergic reuptake inhibitor $N = 17$, neuroleptics $N = 14$. Sixteen of the patients took two different drug and 13 were medication free.

Most of the PTSD patients reported repeated sexual abuse experiences ($N = 31$) which took predominantly place in childhood. Twenty-four had experiences of (repeated) violence and physical abuse. Eighteen patients further reported other traumatic events as accidents, confrontation with suicide, being a witness of violence or war experience.

Table 2 Sociodemographic and clinical characteristics.

Characteristics	PTSD (n = 44)	Controls (n = 65)	Statistics
Age	30.9 (9.6)	31.7 (10.3)	$t_{df107} = -0.67$, $p = .674$
BMI	25.0 (6.8)	23.3 (3.9)	$t_{df103} = 1.36$, $p = .105$
LPS 3 and 4	52.56 (8.7)	57.8 (8.7)	$t_{df106} = -3.16$, $p < .001$
Gender (f/m)	38/6	42/23	$\chi^2_{df1} = 6.359$, $p = .009$
Oral contraceptives (yes/no)	7/31	14/28	$\chi^2_{df1} = 2.292$, $p = .203$
Smoker (yes/no)	28/10	12/30	$\chi^2_{df1} = 16.241$, $p < .001$
BDI sum	26.1 (8.7) 6–46	2.9 (3.4) 0–15	$t_{df105} = 19.27$, $p < .001$
VAS (placebo/hydrocortisone)			ANOVA** main effect group
Stressful	35.9/36.6	28.2/26.4	$F_{df1,103} = 4.48$, $p = .032$
Controllable	62.1/60.9	69.8/68.4	$F_{df1,103} = 3.38$, $p = .068$
	PTSD − MDD* (N = 21)	PTSD + MDD (N = 23)	
PDS total score	30.0 (9.7)	32.5 (7.7)	$t_{df38} = .93$, $p < .360$
BDI sum	26.58 (10.5)	26.53 (7.9)	$t_{df24} = -.38$, $p < .707$

PTSD, posttraumatic stress disorder; BMI, body mass index; BDI, Beck Depression Inventory; PDS, Posttraumatic Stress Diagnostic Scale; LPS, ''Leistungsprüfsystem'' (intelligence test); VAS, visual analog scale; MDD, major depressive disorder.

* Two patients did not answer the PDS.

** Both ANOVAs revealed no main effect of conditions (placebo vs. hydrocortisone) ($p > .65$) or condition by group interaction effect ($p > .60$).

The majority (N = 27) reported two or more different type of trauma.

3.2. Memory retrieval

3.2.1. Word list paradigm

Patients and controls differed in their learning performance in the first day (word list – trial 5: patients 15.5 [3.8], controls 16.9 [2.9], $t_{df104} = -2.186$, $p = .03$). Thus, the percentage of correctly recalled words relative to the words recalled after the fifth learning trial on the day before was analyzed (Terfehr et al., 2011a).

To analyze the effects of hydrocortisone on declarative memory retrieval (word list learning), a 2 × 2 ANOVA with repeated measures was conducted with the main factors group (PTSD patients vs. healthy controls) and condition (placebo vs. hydrocortisone). Data were missing for this test in four control participants (three females, one man) and 8 patients (all female).

We found a significant group by condition interaction effect ($F_{1,95} = 7.207$, $p = .009$), but no main effects of condition or group. Post hoc t-tests for paired samples revealed a significant difference of memory retrieval after hydrocortisone compared to placebo in patients with PTSD ($t_{df36} = -2.056$, $p = .047$), while in the control group this difference did not reach significance ($t_{df61} = 1.718$, $p = .091$). As shown in Fig. 1, PTSD patients showed better memory retrieval after cortisol compared to placebo, which

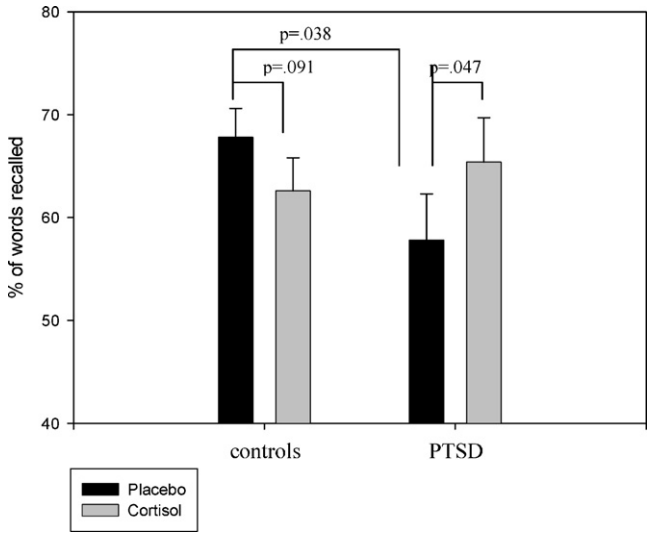

Figure 1 Percentage of words retrieved in the word list paradigm in relation to the last learning list on the previous day (mean [SE]) in patients with PTSD (n = 36) and healthy controls (n = 61) after placebo and after administration of 10 mg hydrocortisone. There was a significant group by condition interaction effect (p = .009).

is an opposing pattern compared to the healthy controls. In the placebo condition controls showed a better memory performance compared to PTSD patients ($t_{df98} = -2.108$, $p = .038$), which was not seen after hydrocortisone administration ($t_{df98} = .448$, $p = .65$) (independent sample t-tests).

Using non-parametric statistics the following results were found: placebo vs. hydrocortisone controls: Wilcoxon $Z = -1.822$, $p = .068$; placebo vs. hydrocortisone PTSD patients: Wilcoxon $Z = 1.650$, $p = .099$; placebo controls vs. PTSD patients: Mann—Whitney $U = 969.5$, $p = .042$; hydrocortisone controls vs. PTSD patients: Mann—Whitney $U = 1086.5$, $p = .572$.

We did not find a significant effect of word valence, group by valence interaction effect or a treatment by valence interaction effect. The three-way interaction also failed to reach significance.

Using AN(C)OVA we analyzed the effects of potentially confounding variables. There were no effects of age ($p = .12$) and BMI ($p = .53$) when introducing these variables as covariates into the analyses. However, there was a significant effect of estimated intelligence (LPS scores) ($p = .004$), but the group by condition interaction effect remained stable in this analysis ($p = .004$). To analyze the influence of gender we introduced this variable as an additional main factor into the ANOVA but did not find a main effect of gender ($p = .11$), a gender by group ($p = .12$), treatment by gender ($p = .20$) or treatment by group by gender interaction effect ($p = .82$). When analyzing only women, we could confirm the significant group by condition interaction effect ($F_{1,67} = 5.184$, $p = .026$). Additionally, a significant effect of the main factor group could be revealed ($F_{1,67} = 4.044$, $p = .048$), suggesting overall worse memory retrieval in the patients. Post hoc t-test revealed no significant difference between placebo and cortisol condition in the controls ($t_{df38} = .826$, $p = .414$). Women with PTSD showed better memory retrieval in the hydrocortisone condition ($t_{df29} = -2.190$, $p = .037$).

Intake of oral contraceptive also failed to reach significance ($p = .621$) as well as smoking ($p = .84$) and medication (yes/no, $p = .46$). Furthermore, we compared PTSD patients with and without major depressive disorder but did not find a significant group effect ($p = .97$). There was an effect of drug condition ($p = .054$) suggesting an improvement in declarative memory retrieval in both groups. Furthermore, using BDI scores as a covariate still showed no effect ($p = .49$). Comparing PTSD patients with and without comorbid borderline personality disorder, we also revealed a main effect of condition ($p = .054$), but no group effect ($p = .25$).

3.2.2. Autobiographical memory test

Again, a 2 × 2 ANOVA with repeated measures was conducted with the main factors group and condition. There were no missing data for the AMT.

There was a trend effect of the main effect of group ($F_{1,107} = 3.400$, $p = .068$), and a significant group by condition interaction effect ($F_{1,107} = 6.859$, $p = .01$). In healthy controls no differences in memory performance after hydrocortisone compared to placebo could be revealed ($t_{df64} = 1.296$, $p = .20$). Again, patients with PTSD performed better after hydrocortisone compared to placebo ($t_{df43} = -2.056$, $p = .01$) (Fig. 2). In accordance with the results in the word list paradigm, controls showed a better memory performance compared to PTSD patients the placebo condition

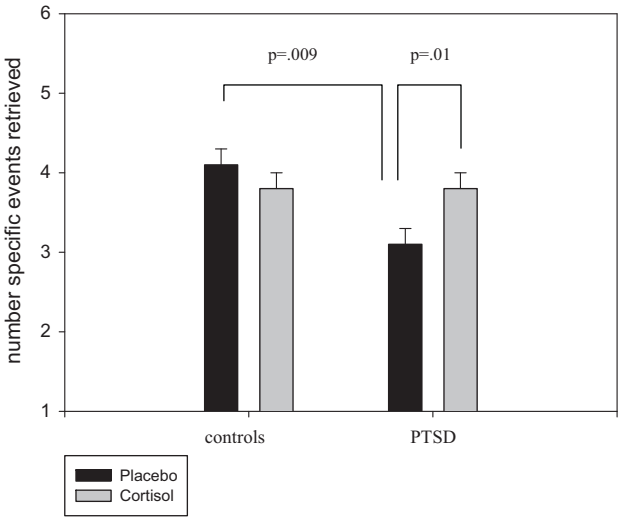

Figure 2 Mean number of specific memories in patients with PTSD ($n = 44$) and healthy controls ($n = 65$) after placebo and hydrocortisone treatment. There was a trend significant effect of the main factor group ($p = .07$) and a significant group by condition interaction effect ($p = .01$).

($t_{df107} = -2.655$, $p = .009$), which was not seen after hydrocortisone administration ($t_{df107} = -.840$, $p = .40$).

Using non-parametric statistics the following results were found: placebo vs. hydrocortisone controls: Wilcoxon $Z = -1.166$, $p = .244$; placebo vs. hydrocortisone PTSD patients: Wilcoxon $Z = 2.431$, $p = .015$; placebo controls vs. PTSD patients: Mann—Whitney $U = 1000.0$, $p = .0072$; hydrocortisone controls vs. PTSD patients: Mann—Whitney $U = 1329.0$, $p = .526$.

Analyses of potential confounders were performed as described above. ANOVA with the additional main factor gender did not reveal any significant effects of this variable (main effect gender: $p = .70$, gender by group $p = .22$, treatment by gender $p = .18$ or treatment by group by gender interaction effect $p = .70$). When analyzing only women, we could confirm the significant group by condition interaction effect ($F_{1,78} = 7.691$, $p = .007$) as well as the effect of the main factor group ($F_{1,78} = 5.481$, $p = .022$). In the control group the difference in memory performance between placebo and cortisol condition did not reach significance (post hoc t-test $t_{df41} = 1.854$, $p = .071$). Women with PTSD showed better memory retrieval in the hydrocortisone condition ($t_{df37} = -2.217$, $p = .033$).

Intake of oral contraceptive ($p = .31$) as well as smoking ($p = .20$) and medication intake ($p = .35$) also did not influence the results. BMI was not found to be a significant covariate ($p = .34$), but there was a significant effect of age ($p = .03$). However, the group by condition interaction effect remained stable in these analyses ($p = .01$). LPS score was also found to be a significant covariate ($p < .001$), but again the group by condition interaction effect was also found in this analysis ($p = .005$).

There were no differences between PTSD patients with and without comorbid MDD ($p = .58$). However, a significant effect of drug condition emerged, showing an improvement in memory retrieval in both groups ($p = .012$). Furthermore, using BDI scores as covariate revealed no effect of

self-reported depressive symptoms ($p = .25$). Comparing PTSD patients with and without borderline personality disorder (BPD) we also see the significant main effect of condition ($p = .01$) as well as a main effect of group ($p = .023$). The group by condition interaction effect failed to reach significance ($p = .14$). Thus, both groups show an improvement of memory specificity after hydrocortisone, but the PTSD without comorbid BPD performed overall worse in this test (PTSD − BPD placebo: 2.6 [1.8] hydrocort: 2.8 [2.0]; PTSD + BPD placebo: 3.6 [1.6] hydrocort: 4.3 [1.6]).

At the end of each test session we used a visual analog scale (0—100) to ask (1) whether the situation was perceived as stressful, and (2) whether the participants had the impression that the situation was controllable. Two repeated measures ANOVA with the main factor groups and condition were performed, one for each question. After placebo as well as after hydrocortisone administration the test situation was rated to be more stressful and less controllable by the patients compared to the controls. However there was no main effect of hydrocortisone on these ratings (see Table 2).

4. Discussion

This study was designed to compare the effects of cortisol on memory retrieval in PTSD patients with those observed in healthy control participants. In both memory-retrieval tasks a condition by group interaction effect occurred. In contrast to healthy participants cortisol had enhancing rather than impairing effects on memory retrieval in patients suffering from PTSD, which was seen for memory specificity in the autobiographical memory test and retrieval of previously learned words. Both tests had been selected because we have previously shown that these paradigms are sensitive to a cortisol induced retrieval impairment in healthy controls (Schlosser et al., 2010; Terfehr et al., 2011a). Despite the substantial difference between the two paradigms we observed a similar response pattern.

4.1. Comparison with previous studies in PTSD

Our results are in line with another study that also shows enhancing effects of cortisol on memory performance in PTSD (Yehuda et al., 2007). Taken these two studies together, there is evidence for enhancing effects of cortisol on memory in PTSD after using a relatively low dosage (10 mg, this study) or a moderate dosage (17.5 mg, Yehuda et al., 2007). Thus, PTSD patients show an enhanced reactivity to exogenous cortisol compared to healthy participants. Contrary to our present findings, two studies did not find effects of glucocorticoids on declarative memory in PTSD (Yehuda et al., 2010; Bremner et al., 2004), while one study found a more pronounced impairment in memory performance in PTSD patients (Grossman et al., 2006).

In sum, only few studies investigated the effects of cortisol on memory, i.e. verbal learning in patients with PTSD. Importantly none of these studies focused on memory retrieval, but instead administered cortisol before memory encoding. Most of these studies investigated small samples in which men were overrepresented (Yehuda et al., 2007, 2010). Only Bremner and colleagues (Bremner et al., 2004) realized a gender balanced sample, while our PTSD sample consists of more women than men. However, there were not only differences to our study concerning the applied memory task (Grossman et al., 2006; Yehuda et al., 2007, 2010) all used the paragraph recall from the Wechsler Memory Scale but also regarding the type and duration of glucocorticoid administration (Bremner et al., 2004). Furthermore, the majority of these studies used a different dosage of hydrocortisone, mostly 17 mg and administered it intravenously in the morning, which are important differences to our study (Grossman et al., 2006; Yehuda et al., 2007, 2010).

4.2. Comparison with previous studies in patients with major depressive disorder and healthy humans

Overall, only few studies investigate the effects of glucocorticoids on memory in psychiatric patients. Due to the fact that major depression is also characterized by HPA axis dysregulations, i.e. reduced rather than enhanced GC sensitivity (Holsboer, 2000), it might be of interest to have a look at findings in these patients in the context of our study. The here presented results contrast with our previous findings in patients with major depressive disorder (MDD). In these patients we found a lack of the impairing effects of hydrocortisone administration on memory retrieval including declarative memory retrieval (Terfehr et al., 2011a), specificity of autobiographic memory (Schlosser et al., 2010) and working memory (Terfehr et al., 2011b). We interpreted these results in MDD in term of reduced GR functioning (Wingenfeld and Wolf, 2011). Combining these studies with the here presented results, it appears that cortisol administration does not influence memory retrieval in patients with MDD, but enhances (declarative) memory retrieval in patients with PTSD.

In line with previous studies in healthy participants (see (Het et al., 2005; de Quervain et al., 2009; Wolf, 2009) for review) we observed impairing effects of cortisol on memory retrieval in the control group. In the current study this effect was apparent only as a trend for retrieval of a word list, but not for autobiographical memory retrieval. Overall the effects in controls appeared to be a little weaker than in our previous studies (Schlosser et al., 2010; Terfehr et al., 2011a,b). Compared to other studies, we only administered a low dosage of hydrocortisone, i.e. 10 mg, which might in part be responsible for the somewhat weaker effects (Het et al., 2005; Young et al., 2011).

4.3. Potential mechanisms

Our results of enhancing rather than impairing effects of cortisol administration on hippocampal based memory retrieval in PTSD suggest an enhanced reactivity to exogenous cortisol in these patients. Due to the fact that additional measurements of HPA axis functioning are missing (e.g. basal cortisol levels, feedback sensitivity, cortisol bioavailability), the interpretation of the data is difficult and remains somewhat speculative.

The effects of glucocorticoids on memory are mostly discussed in the context of GR functioning. The role of GR function in PTSD is still matter of debate. While there is evidence for an enhanced GR sensitivity in PTSD (Yehuda

et al., 1991, 1993, 2004; Rohleder et al., 2004, 2010), other studies did not confirm these results (Pace et al., 2012). Furthermore, there is evidence that early trauma, i.e. history of sexual abuse, may induce epigenetic changes in hippocampal neurons effecting the GR via methylation of the GR gen (McGowan et al., 2009). However, this would rather suggest a decreased GR sensitivity in PTSD. Interestingly, there is evidence that cortisol treatment may reduce involuntary retrieval of traumatic memory, i.e. flashbacks (Aerni et al., 2004). Furthermore, beneficial effects of cortisol have been shown in the context of prevention of PTSD symptoms after acute trauma experiences (Schelling et al., 2001, 2004, 2006). So there is growing evidence for — in part — beneficial effects of cortisol in PTSD. Thus, these beneficial effects, e.g. normalization on hippocampal mediated memory processes should be further investigated.

The current findings of enhanced memory after cortisol treatment in PTSD patients share similarities with recent observations in rodents. Rats which have been exposed to stress early in life display impaired neural plasticity (long term potentiation; LTP) in adulthood. Interestingly, corticosterone treatment enhanced LTP in these animals, while impairing it in the non-stressed control animals (Champagne et al., 2008). Thus, early adversity appears to influence the response of the hippocampus to glucocorticoids in adulthood, most likely via epigenetic mechanisms. Of note, the majority of our PTSD patients reported early trauma. More studies in humans on this topic are warranted.

Alternatively, memory improvement after cortisol administration has been interpreted in the context of inhibition of central corticotropin-releasing hormone (CRH) release through cortisol administration (Yehuda et al., 2007). In PTSD a hypersecretion of CRH has been extensively discussed (Smith et al., 1989; Baker et al., 1999; Kasckow et al., 2001; Yehuda, 2002).

In addition to GR, mineralocorticoid receptors (MR) are important targets for glucocorticoids, with higher binding affinity compared to GR and a high density in the hippocampus (de Kloet, 2000). It has been suggested that GR mediate the impairing effects of cortisol, while MR along with a moderate GR occupation might facilitate hippocampal function (Joels and Krugers, 2007; Ferguson and Sapolsky, 2008). Up to now studies investigating the role of MR function on memory in humans are rare (Otte et al., 2007) and in PTSD patients only few studies investigated the MR at all (Kellner et al., 2002; Otte et al., 2006), suggesting unaltered MR function in these patients. Future studies should investigate the MR/GR balance in PTSD which has been hypothesized to be crucial for neuronal excitability, stress responsiveness, and behavioral adaptation (De Kloet et al., 1998).

4.4. Limitations

Some limitations of this study should be mentioned: one limitation is that we have no data on basal cortisol levels as well as cortisol levels after drug administration, and therefore no treatment check. However, several studies have shown that 10 mg hydrocortisone leads to a substantial increase in salivary cortisol concentrations (Buss et al., 2004).

We have no data on menstrual cycle phase; however, we did not find an effect of gender or intake of oral contraceptives. Future studies should aim to standardize the menstrual cycle phase. Most of our patients suffered from comorbid mental disorders. We analyzed the effect of comorbid depression and borderline personality disorder, which did not alter the results. Similarly, many patients were medicated, which also could have influenced the results (Pariante et al., 2004), which is a limitation of the current study. However, patients with and without medication did not differ.

Even though the significant interaction between cortisol treatment and group membership remained if we controlled for several potential confounds in independent analyses we cannot exclude the possibility that complex interactions between these confounds and/or additional confounds not assessed in our current protocol are partially responsible for the observed effects. A replication of the current findings in a different PTSD population is therefore warranted.

It would be of interest to combine our experimental design with direct measurements of GR functioning, HPA axis feedback sensitivity, basal cortisol levels and neuroimaging as done by others (Yehuda et al., 2010). Furthermore, it would be helpful for the interpretation of the data to measure GC levels after hydrocortisone administration. In the autobiographic memory test, it would have been interesting to obtain ratings on emotionality and vividness of the retrieved memories, as well as information about remoteness, as autobiographical memories are mostly rated to be more emotional and vivid compared to laboratory stimuli like words (Cabeza and St. Jacques, 2007). In both tests it would be also helpful to have ratings about the arousal of the presented stimuli, which might have also influenced the results. However, it is in general difficult to evoke strong arousal by presenting words and it would be helpful to have measurement of the sympathetic nervous system.

4.5. Outlook

In conclusion the current results indicate that cortisol has opposing effects on memory retrieval in healthy controls compared to patients with PTSD. In PTSD patients memory retrieval was enhanced rather than impaired by cortisol. This might reflect enhanced hippocampal functions after cortisol treatment in these patients. The increased ability to voluntarily retrieve previously learned information might very well be paralleled by a reduction in involuntarily retrieved traumatic memories (flashbacks). Interestingly, there is some evidence that hydrocortisone treatment might be an effective pharmacological treatment opportunity (Aerni et al., 2004) as well as a useful prevention strategy after acute trauma experiences (Schelling et al., 2001, 2004, 2006). In these studies cortisol treatment seems to reduce involuntary retrieval of traumatic memory, i.e. flashbacks. Possibly, this is accompanied by an increased capability of voluntary memory retrieval.

Role of funding source

This study was supported by a grant from the Deutsche Forschungsgemeinschaft (WI 3396/1-1) awarded to KW, OTW and MD.

Conflict of interest

There were no conflicts of interest, financial or otherwise, to declare.

Acknowledgements

We would like to thank all subjects for their participation in the present study.

Appendix A

Adjectives used in the two parallel versions of the AMT (translated from German).

	Positive	Negative	Neutral
Version A	Happy	Angry	Concentrated
	Interested	Hurt	Busy
Version B	Safe	Sad	Patient
	Successful	Clumsy	Correct

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