Psychopharmacology (2011) 215:71–79
DOI 10.1007/s00213-010-2117-z

ORIGINAL INVESTIGATION

Hydrocortisone impairs working memory in healthy humans, but not in patients with major depressive disorder

Kirsten Terfehr · Oliver Tobias Wolf · Nicole Schlosser · Silvia Carvalho Fernando · Christian Otte · Christoph Muhtz · Thomas Beblo · Martin Driessen · Carsten Spitzer · Bernd Löwe · Katja Wingenfeld

Received: 1 October 2010 / Accepted: 24 November 2010 / Published online: 16 December 2010

Abstract
Objective Several studies have shown that stress or the administration of glucocorticoids can impair hippocampus-based declarative memory retrieval and prefrontal dependent working memory performance in healthy subjects. Major Depressive Disorder (MDD) is often characterized by memory impairment and increased cortisol secretion. Studies indicate that the impairing effects of glucocorticoids on declarative memory performance are missing in patients with MDD. The purpose of our study was to investigate whether the finding of missing effects of acute cortisol administration on memory performance in MDD is also seen when examining prefrontal-based working memory.

Methods In a placebo-controlled study, 57 patients with MDD and 56 sex- and age-matched healthy control subjects received either placebo or 10 mg of hydrocortisone orally before memory testing. To test the verbal modality of working memory, the Word Suppression Test was applied with one negative and one neutral test part.
Results After hydrocortisone intake, healthy subjects showed a significantly poorer working memory performance compared to placebo treatment when negative interference words were administered. In contrast, memory performance of MDD patients was not affected by hydrocortisone treatment.
Conclusions The missing effects of glucocorticoid administration on working memory in MDD might be interpreted in the context of reduced central glucocorticoid receptor function.

Keywords Depression · Working memory · Cortisol · HPA axis

K. Terfehr · C. Spitzer · B. Löwe · K. Wingenfeld
Department of Psychosomatic Medicine and Psychotherapy, University Medical Center Hamburg-Eppendorf & Schön Klinik Hamburg-Eilbek, Hamburg, Germany

O. T. Wolf
Department of Cognitive Psychology, University of Bochum, Bochum, Germany

N. Schlosser · S. C. Fernando · T. Beblo · M. Driessen
Department of Psychiatry and Psychotherapy Bethel, Ev. Hospital Bielefeld, Bielefeld, Germany

C. Otte · C. Muhtz
Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

K. Wingenfeld (✉)
Department of Psychosomatic Medicine and Psychotherapy, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany
e-mail: k.wingenfeld@uke.uni-hamburg.de

Introduction

One major system responding to stress is the hypothalamic-pituitary-adrenal (HPA) axis, which initiates, when activated, the secretion of glucocorticoids (GCs) from the adrenal cortex. GCs can pass the blood brain barrier and act in the brain via binding to mineralocorticoid receptors (MR or type I) and glucocorticoid receptors (GR or type II), which exhibit their highest density in regions relevant for cognition and memory, such as the hippocampal area and the prefrontal cortex (de Kloet 2003; Lupien and Lepage 2001). The hippocampus is especially important for declarative memory (Eichenbaum et al. 1999; Squire 1992), while prefrontal brain areas like the dorsolateral prefrontal cortex and the

anterior cingulate gyrus are crucial for working memory (WM; Baddeley 2001).

GCs have been repeatedly found to impair declarative memory retrieval in humans and animals. De Quervain and colleagues were the first to show in rodents that stress or GC treatment impaired memory retrieval (de Quervain et al. 1998). These findings have been replicated by others (Diamond et al. 2006) and similarly shown for humans (de Quervain et al. 2000; Kirschbaum et al. 1996; Kuhlmann et al. 2005a; Wolf et al. 2001). Moreover, psychosocial stress-induced cortisol elevations led to poorer declarative memory performance (Buchanan et al. 2006; Kuhlmann et al. 2005b; Lupien et al. 1997).

The effects of stress and stress hormones on healthy human subjects have also been investigated for prefrontal dependent WM, even though the empirical situation is rather heterogeneous. The prefrontal cortex seems to be a significant target for the negative feedback actions of GCs, indicating that this area could play a significant role in the acute effects of GCs on cognitive function (Lupien et al. 1999). WM is the cognitive mechanism that allows us to keep a limited amount of information active for a limited period of time (Baddeley 1995) and is furthermore thought to be crucial for reducing distraction by suppressing irrelevant information (Baddeley and Della Sala 1996). As shown for declarative memory performance, animal studies revealed that chronic stress or GC treatment also impair WM (Arnsten 2000; Cerqueira et al. 2007; Mizoguchi et al. 2000; Shansky et al. 2006). In humans, pharmacological studies observed that both acute (Lupien et al. 1999; Wolf et al. 2001) and chronic cortisol administration (Young et al. 1999) led to poorer WM performance, although not all studies agree (Monk and Nelson 2002; Oei et al. 2009; Porter et al. 2002). In addition, studies in healthy subjects found that acute psychosocial stress-induced GC elevations are related to impaired WM performance (Oei et al. 2006; Schoofs et al. 2008, 2009), while others did not find deficits in WM after psychosocial stress (Kuhlmann et al. 2005b; Smeets et al. 2006).

The influence of emotional arousal or emotional valence of the learning material in WM tasks has been investigated repeatedly (Dolcos et al. 2008; Dolcos and McCarthy 2006; Kensinger and Corkin 2003). For example, Dolcos and McCarthy (2006) found that emotional distractors evoked strong activity in typical emotional processing regions (amygdala and ventrolateral prefrontal cortex), while WM regions were relatively deactivated, which led to impaired WM performance. The coactivation of the beta-adrenergic system is also believed to be an important determinant of GC effects on memory in humans (Cahill et al. 1994; de Quervain et al. 2007; Roozendaal et al. 2006b). This has recently been demonstrated with pharmacological manipulations (beta-blockade; de Quervain et al. 2007). Furthermore, in rats, it was shown that both propranolol treatment and lesions of the basolateral amygdala blocked the negative effects of cortisone on WM performance (Roozendaal et al. 2004). Nonetheless, most human studies on GC effects on memory have used relatively neutral learning material (digits or numbers).

A role of HPA axis alternations has been proposed for several psychiatric disorders, as Major Depressive Disorder (MDD). HPA axis dysregulation, e.g., enhanced basal and stimulated cortisol release as well as high cortisol levels after dexamethasone (DEX) administration, are the most consistent findings in patients with MDD (Musselmann et al. 1998; Pariante and Lightman 2008; Parker et al. 2003; Plotsky et al. 1998). Furthermore, impairments in hippocampal-based declarative memory are frequently reported in MDD patients (Brand et al. 1992; Burt et al. 1995; Veiel 1997). Several studies have linked the increased basal cortisol levels to impaired cognitive functions in depressed patients (Belanoff et al. 2001; Hinkelmann et al. 2009). For example, Hinkelmann et al (2009) found a negative correlation between salivary cortisol levels and hippocampus-related neuropsychological domains (e.g., verbal memory, visuospatial memory) and executive function (e.g., working memory). Accordingly, in prefrontal brain areas, a decrease in GR mRNA density has been found in depressed patients (Webster et al. 2002). Recently, we investigated the effect of acute cortisol administration on declarative memory and found reduced memory performance in healthy controls after cortisol intake, while the administration of cortisol in patients with MDD did not further reduce declarative memory retrieval. This might indicate a reduced central glucocorticoid receptor functioning (Schlosser et al. 2010; Terfehr et al. in press). However, to our knowledge, no study has examined the effects of acute glucocorticoid administration on WM in MDD by now.

The purpose of this study was to investigate whether the finding of missing effects of acute cortisol administration on WM in MDD is restricted to hippocampal-based declarative memory performance, as shown in our previous studies, or is also seen when examining prefrontal-based WM. We hypothesized first, that healthy control subjects show impairments in working memory performance following acute cortisol administration. Our second hypothesis was that due to reduced GR sensitivity acute cortisol elevation would have no effect on memory performance in depressed patients. Third, we hypothesized that depressed patients show an overall reduced working memory performance compared to healthy controls. Since stress and GCs have been shown to impair WM performance especially when distractors were emotionally arousing, we hypothesized that emotionally arousing stimuli impair WM performance to a higher degree than neutral irrelevant distractors.

Methods and material

Subjects

Fifty-seven inpatients with MDD and 56 age- and gender-matched healthy control subjects participated in the study. All patients were recruited at the Department of Psychiatry and Psychotherapy Bethel (Ev. Hospital Bielefeld, Germany), at the Department of Psychosomatic Medicine and Psychotherapy and the Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf & Schön Klinik Hamburg-Eilbek, Germany, and met the DSM-IV criteria for major depression. Exclusion criteria for all inpatients and control subjects were the following: 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., Morbus Cushing), immune-mediated diseases, medicated hypertension, severe cardiovascular diseases, or current infections. Further exclusion criteria were pregnancy, the use of beta-blockers or benzodiazepines, current anorexia, current or lifetime schizophrenia, alcohol or drug dependence, bipolar disorder, schizoaffective disorder, attention-deficit hyperactivity disorder or cognitive impairment. Intake of antidepressants did not lead to exclusion.

Control subjects were recruited by local advertising and received remuneration for their efforts (100€). Written informed consent was obtained from all subjects. The study was approved by the University of Muenster Ethics Committee and the Ethics Committee Hamburg.

Procedure

Diagnoses were made using the Structured Clinical Interview for DSM-IV, SCID-I for Axis-I disorders (Wittchen et al. 1997), which was also administered for healthy controls. Severity of depressive symptoms at the time of assessment was evaluated using the Beck-Depression Inventory (Beck and Steer 1994).

To test the verbal modality of working memory, we administered the self-developed Word Suppression Test (WST) in the style of the Wechsler Memory Scale-Revised (Wechsler 1987), which was administered among other neuropsychological tests. The WST consisted of two test parts (one with negative and one with neutral interference words), presented in randomized order. In each test part 14 recorded trials with a series of alternately presented digits and interference words were presented verbally. In the easiest trials, a series consisted of two digits and two words, while in the hardest trials, a series consisted of eight digits and eight words. By two series consisted of the same number of digits and words (e.g., series one and two consisted of two digits and two words, series three and four consisted of three digits and three words…). Digits and words were presented at a rate of one per second. The task was finished when a subject failed to reproduce two trials of the same length. There was no time limit set, while the whole test did not take longer than 10 min. Analogous to the Wechsler Memory Scale-Revised (Wechsler 1987), the WST score represented a cumulative raw score, with one point given for each correctly reproduced sequence. All interference words were taken from Borsutzky et al. (unpublished). This study provides statistical norms of 551 German nouns, considering the word's familiarity, emotional valence, imagery, and frequency.

Each participant was tested once with the negative and the neutral version of the WST after receiving either a dosage of 10 mg hydrocortisone (MDD: $n = 30$; controls: $n = 27$) or a placebo (MDD: $n = 27$; controls: $n = 29$). Drugs were administered orally 1 h prior to memory testing, which took place between 1600 and 1800 hours. Saliva was collected 10 min before (T1), 45 min (T2), and 90 min (T3) after cortisol administration, using saliva collection devices (Sarstedt, Rommelsdorf, Germany). All biochemical analyses were done by the Department of Biological Psychiatry, University Medical Center Hamburg-Eppendorf. Interassay and intraassay coefficients of variation were below 8%.

Statistical analysis

Demographic data were analyzed using Pearson's Chi² test for categorical data and Student's t test for continuous data. Salivary cortisol was analyzed using analysis of variance (ANOVA) with repeated measurements. Bonferroni-adjusted post hoc analyses were used in case of a significant group effect. Effects of hydrocortisone on working memory were analyzed using t tests. All statistical procedures were performed with the "Statistical Package for the Social Science 15.0" (SPSS 15.0).

Results

Demographic and clinical data

Patients and controls did not differ concerning age, sex, and years of education (Table 1). Seventeen patients had a current comorbid diagnosis of anxiety disorder. Forty were treated with antidepressant medication (SNRI = 15, tetracyclic antidepressants = 4, SSRI = 21). All healthy subjects were free of medication and had no psychiatric diagnosis.

Cortisol levels

Cortisol measurements could be conducted for 70 subjects ($n = 33$ in the placebo condition, $n = 37$ in the cortisol condition). A 2 × 3 ANOVA with repeated measures was

Table 1 Sociodemographic and clinical characteristics

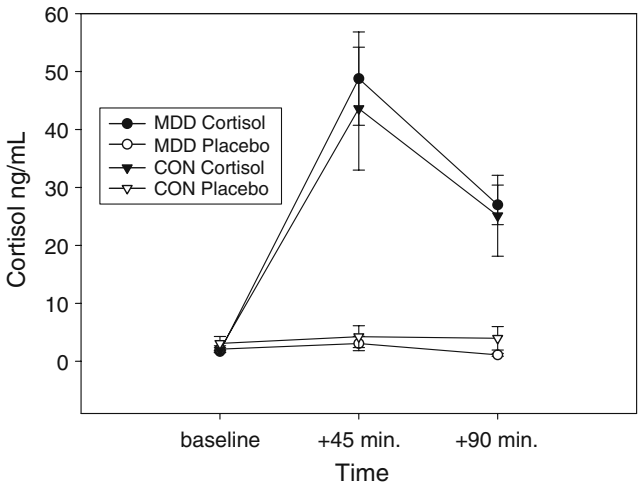
Characteristics	MDD (n = 57)	Controls (n = 56)	Statistics
Age	34.26 (9.19)	32.36 (10.56)	$t_{111} = 1.02$, $p = .309$
Sex	61,4 % female	63,8 % female	$\chi^2 = 0.75$, $p = .846$
Years of formal school education	11.19 (1.56)	11.60 (1.52)	$t_{111} = -1.30$, $p = .197$
BDI sum	21.84 (10.68)	2.678 (3.61)	$t_{103} = 12.63$, $p < .001$

MDD Major Depressive Disorder; *BDI* Beck Depression Inventory

performed with time (T1, T2, T3) and treatment (placebo vs. cortisol) as main factors. A significant treatment effect could be revealed, reflecting increased saliva cortisol levels after administration of hydrocortisone compared to placebo ($F_{1,68}$ = 42.60, p < .001). Furthermore, there was a significant time effect ($F_{2,136}$ = 34.58, p < .001), as well as a significant treatment by time interaction effect ($F_{2,136}$ = 33.46, p < .001), showing significant increase of saliva cortisol levels only after hydrocortisone administration. Accordingly, cortisol levels at baseline did not differ between placebo and cortisol treatment (t_{68} = −.64, p = .526), while cortisol levels were significantly higher at T2 (t_{68} = −6.66, p < .001) and T3 (t_{68} = −6.55, p < 001) after hydrocortisone treatment. Furthermore, we did not find any significant difference between patients and controls at each measurement point (Fig. 1).

Working memory

To analyze the effects of hydrocortisone on WM performance, four separate independent group t tests were conducted for each version (neutral and negative) of the WST. Due to multiple testing, levels of significance were corrected to alpha = .05/4 = 0.01.



Note. MDD = Major Depressive Disorder; CON = Controls

Fig. 1 Mean (SE) saliva cortisol levels in patients with MDD (placebo n = 15; cortisol n = 23) and healthy control subjects (placebo n = 18; cortisol n = 14) after placebo and hydrocortisone administration. ANOVA revealed that cortisol levels were higher after 10 mg hydrocortisone compared to placebo. *MDD* Major Depressive Disorder; *CON* controls

WST with neutral interference words

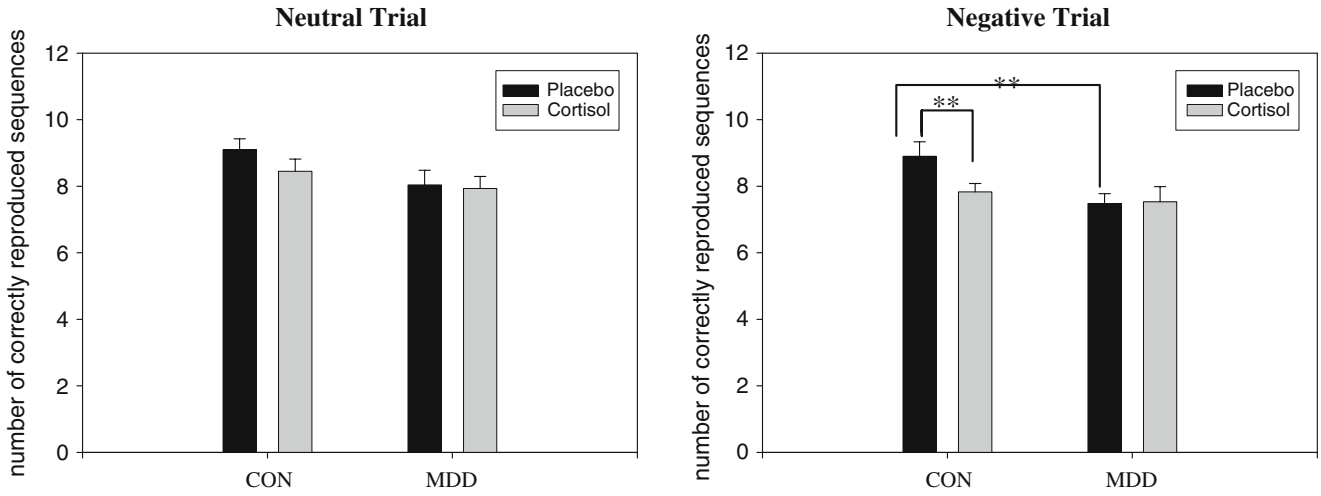
Analyses revealed no impairment of memory performance after hydrocortisone administration compared to placebo in the control group (t_{54} = 1.05, p = .299), as well as in the MDD group (t_{55} = .18, p = .855; Fig. 2). In the placebo condition, depressed patients did not differ significantly from control subjects (t_{54} = −1.98, p = .053). Furthermore, after hydrocortisone treatment, there was no significant difference concerning WM performance between the two groups (t_{55} = −1.28, p = .207). Antidepressant medication had no effect on memory performance in the neutral condition. There was no significant difference between medicated and unmedicated patients in WM performance (t_{55} = 1.28, p = .204).

WST with negative interference words

While hydrocortisone treatment did not impair WM performance in depressed patients (t_{55} = −.08, p = .935), healthy control subjects showed a significantly lower WM performance after hydrocortisone administration compared to placebo (t_{54} = 2.94, p = .005; Fig. 2). Additionally, patients suffering from MDD showed a significant poorer WM performance in the placebo condition compared to healthy control subjects (t_{54} = −2.73, p = .009). After hydrocortisone treatment, WM performance did not differ between the two groups (t_{55} = −.58, p = .564). As well as in the neutral trial, antidepressant medication had no effect on memory performance in the negative trial (t_{55} = 1.14, p = .258).

Additional analyses

There was no significant difference in WM performance of healthy control subjects in the placebo condition between the neutral and the negative test version (t_{28} = .64, p = .527). In contrast, MDD patients showed a significant poorer memory performance in the negative version of the placebo condition compared to the neutral version (t_{26} = 2.155, p = .041).



*Note. ** = p<.01; MDD = Major Depressive Disorder; CON = Controls*

Fig. 2 Number of correctly reproduced sequences (mean [SE]) in patients with MDD (hydrocortisone n = 30, placebo n = 27) and healthy control subjects (hydrocortisone n = 27, placebo n = 29) after placebo and after administration of 10 mg hydrocortisone in the neutral and negative trial. In contrast to MDD patients, healthy controls showed an impaired memory performance after hydrocortisone administration compared to placebo when negative distractors were used. **p < .01; *MDD* Major Depressive Disorder; *CON* controls

Discussion

The results of this study revealed that in healthy controls, hydrocortisone administration led to a significant poorer WM performance when negative distractors were used, while in the neutral test trial, there were no impairing effects of cortisol on WM. In MDD, acute cortisol administration had no effect on WM performance in both conditions. In addition, depressed patients showed an overall reduced WM performance compared to healthy controls.

Our result of impaired WM performance after acute cortisol administration in healthy subjects is in line with other pharmacological studies investigating the effect of acute (Lupien et al. 1999) and chronic (Young et al. 1999) hydrocortisone administration on WM, although not all studies agree (Monk and Nelson 2002; Porter et al. 2002; Wolf et al. 2001). One possible explanation for the diverging results is the administered dose of hydrocortisone. The latter studies used nearly comparable doses of hydrocortisone (app. 35–40 mg), while in our study, we administered only a dose of 10 mg hydrocortisone, which is more comparable to a physiological cortisol increase after stress induction. Especially those studies, which investigated WM performance after stress-induced GC elevations, showed that a moderate but physiological cortisol enhancement had impact on WM in humans (Luethi et al. 2008; Oei et al. 2006; Robinson et al. 2008; Schoofs et al. 2008), although not all studies agree (Kuhlmann et al. 2005b; Smeets et al. 2006). Another explanation for the contradicting results obtained in some of the previous studies might be the employment of different WM paradigms (item recognition task, *n*-back task, reading span task), varying in sensitivity, in involvement of WM processes and in the demand they place on WM. Another aspect which might explain the diverging findings is the emotionality of the learning material.

Our study revealed that the administration of GCs led to significant impairment on WM only when distractors were emotionally valenced. This is in line with other studies on declarative memory performance, showing that cortisol significantly impaired retrieval of negative words, while in contrast, it had only a minor or no effect on neutral words (de Quervain et al. 2007; Kuhlmann et al. 2005a). To our knowledge, only Oei et al. (2009) investigated the effect of GCs on WM in healthy human subjects, using emotional and neutral distractors by now. They found that, contrary to our and previous findings of impairing effects of cortisol on WM, hydrocortisone reduces the distractions by emotional stimuli. However, because of a different WM paradigm and a higher dose of hydrocortisone, a comparison to our study is hardly possible.

Roozendaal et al. (2004) have dissected the underlying mechanisms of emotional memory impairment after GC administration. They found that for the effects of GCs, noradrenergic activation in the basolateral nucleus (BLA) is a prerequisite. BLA lesions as well as beta-blockade prevent the effects of GC agonists on memory (de Quervain et al.

2007; Roozendaal et al. 2006a, b). Thus, in further research, the effect of GCs on WM performance should be investigated with regard to the emotionality of the learning material as well as to the different doses of hydrocortisone administration.

The missing impairing effects in depressed patients in WM performance are in line with recent findings from our working group (Schlosser et al. 2010; Terfehr et al. in press) and others (Bremner et al. 2004), investigating the effect of acute cortisol administration on declarative and autobiographical memory performance. This missing impairment in WM after hydrocortisone administration might be discussed in the context of reduced GR sensitivity in MDD (Rohleder et al. 2010). Investigations, using the DEX suppression test and the combined DEX/CRF test in MDD, showed a reduced feedback sensitivity of GRs. Nemeroff (1996) has provided evidence that an increased central CRH drive is at the core of this phenomenon. Pariante et al. (2004) suggest that the brain is in a state of GC resistance. They demonstrated that GR signaling is reduced in depression. Other authors postulate that deficient GRs are responsible for the reduced feedback sensitivity in MDD (Holsboer 2000). As described above, GRs exhibit, among others, a high density in the prefrontal cortex, which is crucial for WM (Baddeley 2001). Interestingly, in this brain region, reduced GR mRNA has been found in depressed patients (Webster et al. 2002). Therefore, the missing effects of cortisol on WM in MDD might be due to reduced functioning of prefrontal GRs, while MR-mediated effects can currently not be ruled out.

Furthermore, stress research revealed evidence for epigenetic effects on the GRs. Adverse childhood experience seems to imprint itself in genomic regulation of the stress system, e.g., increased methylation of the GR promoter region and decreased levels of GR transcripts (McGowan et al. 2009). Early stress in turn is a potent risk factor for developing depression, which might suggest that epigenetic changes are associated with enhanced vulnerability for MDD (Heim et al. 2008b; Holsboer and Ising 2010). This is underlined by studies on bipolar disorders, where GR mRNA changes were not restricted to depressive states, but continued after recovery (Matsubara et al. 2006). Other colleagues argued that some patients showed escape from dexamethasone suppression after CRF after successful treatment. The latter findings might reflect a trait-like marker of depression risk (Heim et al. 2008a). In support of this hypothesis, asymptomatic first-degree relatives of patients with MDD exhibit increased cortisol responses in the DEX/CRF test over time (Holsboer et al. 1995; Modell et al. 1998). On the other hand, there exist several studies, indicating that HPA disturbances normalize with successful treatment or remission (Ising et al. 2005; Kunugi et al. 2006; Van Den Eede et al. 2006). Thus, there are more investigations needed to shed light on this topic.

Our findings may also have clinical implications, as they provide further evidence for a potential GR dysfunction in MDD patients. As mentioned above, it has been shown that remission from depression is associated with normalization of HPA axis dysfunction (Charles et al. 1982). Thus, several pharmacological approaches aim to reduce HPA axis activity (Berton and Nestler 2006; Schule et al. 2009). These new therapy strategies include CRH1 receptor antagonists (e.g., R121919, Antarlamin), antagonism at vasopressin V1b receptors (e.g., SSR149415), inhibition of cortisol synthesis, (e.g., metyrapone, ketoconazole), antiglucocorticoid treatment with dehydroepiandrosterone, and treatment with glucocorticoid receptor antagonists (e.g., mifepristone, Org 34517; for recent reviews, see Berton and Nestler 2006; Schule et al. 2009; Thomson and Craighead 2008). To date, only one study has investigated the impact of antiglucocorticoids (mifepristone) on cognitive function (spatial working memory, verbal fluency, spatial recognition) in mood disorder and found these cognitive functions to be significantly improved with mifepristone, irrespective of improvement of depressive symptoms (Young et al. 2004). This might indicate a restoration of GR function initiated by the drug and a subsequently appropriate MR/GR balance which enhances cognitive performance. However, despite these first promising results of antiglucocorticoid treatment, the evidence for clinical efficacy of drugs influencing HPA system regulation is still limited. Therefore, it is not clear, at present, to what extent new antidepressant treatment options derived from the corticoid receptor hypothesis will be accepted in treating depression in future.

Some limitations of our study should be mentioned. First, we did not assess subjective valence and arousal ratings of the distractors. Therefore, we cannot determine whether the negative distractors would have been rated as more arousing as the neutral ones or whether patients and controls would have differed in their rating. In addition, the majority of our patients were medicated, which could have had an influence on the HPA axis functioning, GR sensitivity as well as memory performance (Pariante et al. 2004), although medicated and unmedicated patients did not significantly differ in their memory performance. Therefore, in the future, it would be interesting to investigate the effects of hydrocortisone on WM in a sample of medication free patients. Furthermore, we did not ascertain data on duration of medication, which might be helpful to be considered in future research. Additionally, we did not assess if control subjects had a first degree relative with psychiatric illness, since memory deficits are also found in first degree relatives (Quraishi et al. 2009). As there exist diverging findings on the effects of GCs on WM performance, it might be interesting to investigate whether the effects of hydrocortisone on WM are mediated by the

complexity of the material or different doses of hydrocortisone. Nevertheless, in comparison to most other studies investigating the effect of GCs on memory, we had a relatively tall sample size (56 healthy controls, 57 MDD). Finally, concerning the lack of cortisol effect on memory performance in MDD, a floor effect cannot be fully excluded but appears unlikely since patients and controls on average reached at least five digits.

In sum, this is the first study examining the effect of acute cortisol administration on WM performance in patients with MDD with neutral and emotional valenced distractors. In healthy control subjects, the administration of hydrocortisone led to a significant impairment in WM performance when negative distractors were used, while in MDD, this effect was absent. Thus, the administration of hydrocortisone did not further impair WM performance in MDD patients. Nevertheless, future studies are needed to further characterize the role of the emotional content of the dose of hydrocortisone as well as of the different stress paradigms.

Acknowledgments The work of the authors is supported by grants from the German Research Foundation (DFG WI3396/2-1 and WO 733/6-2).

References

Arnsten AF (2000) Stress impairs prefrontal cortical function in rats and monkeys: role of dopamine D1 and norepinephrine alpha-1 receptor mechanisms. Prog Brain Res 126:183–192

Baddeley (1995) Working Memory: the interface between memory and cognition. In: Schacter DL, Tulving E (eds) Memory systems. MIT, Cambridge, pp 351–368

Baddeley (2001) Is working memory still working? Am Psychol 56 (11):851–864

Baddeley, Della Sala S (1996) Working memory and executive control. Philos Trans R Soc Lond B Biol Sci 351(1346):1397–1403, discussion 1403-1394

Beck AT, Steer RA (1994) Beck-depressions-inventar: BDI. Testhandbuch. Huber, Bern

Belanoff JK, Kalehzan M, Sund B, Fleming Ficek SK, Schatzberg AF (2001) Cortisol activity and cognitive changes in psychotic major depression. Am J Psychiatry 158(10):1612–1616

Berton O, Nestler EJ (2006) New approaches to antidepressant drug discovery: beyond monoamines. Nat Rev Neurosci 7(2):137–151

Brand AN, Jolles J, Gispen-de Wied C (1992) Recall and recognition memory deficits in depression. J Affect Disord 25(1):77–86

Bremner JD, Vythilingam M, Vermetten E, Anderson G, Newcomer JW, Charney DS (2004) Effects of glucocorticoids on declarative memory function in major depression. Biol Psychiatry 55 (8):811–815

Buchanan TW, Tranel D, Adolphs R (2006) Impaired memory retrieval correlates with individual differences in cortisol response but not autonomic response. Learn Mem 13(3):382–387

Burt DB, Zembar MJ, Niederehe G (1995) Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. Psychol Bull 117(2):285–305

Cahill L, Prins B, Weber M, McGaugh JL (1994) Beta-adrenergic activation and memory for emotional events. Nature 371 (6499):702–704

Cerqueira JJ, Mailliet F, Almeida OF, Jay TM, Sousa N (2007) The prefrontal cortex as a key target of the maladaptive response to stress. J Neurosci 27(11):2781–2787

Charles G, Wilmotte J, Quenon M, Mendlewicz J (1982) Reproducibility of the dexamethasone suppression test in depression. Biol Psychiatry 17(7):845–848

de Kloet ER (2003) Hormones, brain and stress. Endocr Regul 37 (2):51–68

de Quervain DJ, Roozendaal B, McGaugh JL (1998) Stress and glucocorticoids impair retrieval of long-term spatial memory. Nature 394(6695):787–790

de Quervain DJ, Roozendaal B, Nitsch RM, McGaugh JL, Hock C (2000) Acute cortisone administration impairs retrieval of long-term declarative memory in humans. Nat Neurosci 3(4):313–314

de Quervain DJ, Aerni A, Roozendaal B (2007) Preventive effect of beta-adrenoceptor blockade on glucocorticoid-induced memory retrieval deficits. Am J Psychiatry 164(6):967–969

Diamond DM, Campbell AM, Park CR, Woodson JC, Conrad CD, Bachstetter AD et al (2006) Influence of predator stress on the consolidation versus retrieval of long-term spatial memory and hippocampal spinogenesis. Hippocampus 16(7):571–576

Dolcos F, McCarthy G (2006) Brain systems mediating cognitive interference by emotional distraction. J Neurosci 26(7):2072–2079

Dolcos F, Diaz-Granados P, Wang L, McCarthy G (2008) Opposing influences of emotional and non-emotional distracters upon sustained prefrontal cortex activity during a delayed-response working memory task. Neuropsychologia 46(1):326–335

Eichenbaum H, Dudchenko P, Wood E, Shapiro M, Tanila H (1999) The hippocampus, memory, and place cells: is it spatial memory or a memory space? Neuron 23(2):209–226

Heim C, Mletzko T, Purselle D, Musselman DL, Nemeroff CB (2008a) The dexamethasone/corticotropin-releasing factor test in men with major depression: role of childhood trauma. Biol Psychiatry 63(4):398–405

Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB (2008b) The link between childhood trauma and depression: insights from HPA axis studies in humans. Psychoneuroendocrinology 33 (6):693–710

Hinkelmann K, Moritz S, Botzenhardt J, Riedesel K, Wiedemann K, Kellner M et al (2009) Cognitive impairment in major depression: association with salivary cortisol. Biol Psychiatry 66 (9):879–885

Holsboer F (2000) The corticosteroid receptor hypothesis of depression. Neuropsychopharmacology 23(5):477–501

Holsboer F, Ising M (2010) Stress hormone regulation: biological role and translation into therapy. Annu Rev Psychol 61(81–109): C101–C111

Holsboer F, Lauer CJ, Schreiber W, Krieg JC (1995) Altered hypothalamic-pituitary-adrenocortical regulation in healthy subjects at high familial risk for affective disorders. Neuroendocrinology 62(4):340–347

Ising M, Kunzel HE, Binder EB, Nickel T, Modell S, Holsboer F (2005) The combined dexamethasone/CRH test as a potential surrogate marker in depression. Prog Neuropsychopharmacol Biol Psychiatry 29(6):1085–1093

Kensinger EA, Corkin S (2003) Effect of negative emotional content on working memory and long-term memory. Emotion 3(4):378–393

Kirschbaum C, Wolf OT, May M, Wippich W, Hellhammer DH (1996) Stress- and treatment-induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. Life Sci 58(17):1475–1483

Kuhlmann S, Kirschbaum C, Wolf OT (2005a) Effects of oral cortisol treatment in healthy young women on memory retrieval of negative and neutral words. Neurobiol Learn Mem 83(2):158–162

Kuhlmann S, Piel M, Wolf OT (2005b) Impaired memory retrieval after psychosocial stress in healthy young men. J Neurosci 25 (11):2977–2982

Kunugi H, Ida I, Owashi T, Kimura M, Inoue Y, Nakagawa S et al (2006) Assessment of the dexamethasone/CRH test as a state-dependent marker for hypothalamic-pituitary-adrenal (HPA) axis abnormalities in major depressive episode: a Multicenter Study. Neuropsychopharmacology 31(1):212–220

Luethi M, Meier B, Sandi C (2008) Stress effects on working memory, explicit memory, and implicit memory for neutral and emotional stimuli in healthy men. Front Behav Neurosci 2:5

Lupien SJ, Lepage M (2001) Stress, memory, and the hippocampus: can't live with it, can't live without it. Behav Brain Res 127(1–2):137–158

Lupien SJ, Gaudreau S, Tchiteya BM, Maheu F, Sharma S, Nair NP et al (1997) Stress-induced declarative memory impairment in healthy elderly subjects: relationship to cortisol reactivity. J Clin Endocrinol Metab 82(7):2070–2075

Lupien SJ, Gillin CJ, Hauger RL (1999) Working memory is more sensitive than declarative memory to the acute effects of corticosteroids: a dose-response study in humans. Behav Neurosci 113(3):420–430

Matsubara T, Funato H, Kobayashi A, Nobumoto M, Watanabe Y (2006) Reduced glucocorticoid receptor alpha expression in mood disorder patients and first-degree relatives. Biol Psychiatry 59(8):689–695

McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonte B, Szyf M et al (2009) Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci 12(3):342–348

Mizoguchi K, Yuzurihara M, Ishige A, Sasaki H, Chui DH, Tabira T (2000) Chronic stress induces impairment of spatial working memory because of prefrontal dopaminergic dysfunction. J Neurosci 20(4):1568–1574

Modell S, Lauer CJ, Schreiber W, Huber J, Krieg JC, Holsboer F (1998) Hormonal response pattern in the combined DEX-CRH test is stable over time in subjects at high familial risk for affective disorders. Neuropsychopharmacology 18(4):253–262

Monk CS, Nelson CA (2002) The effects of hydrocortisone on cognitive and neural function: a behavioral and event-related potential investigation. Neuropsychopharmacology 26(4):505–519

Musselmann DL, DeBattista C, Nathan KI, Kilts CD, Schatzberg AF, Nemeroff CB (1998) Biology of mood disorders. In: Schatzberg AF, Nemeroff CB (eds) Textbook of psychopharmacology, 2nd edn. American Psychiatry Press, Arlington

Nemeroff CB (1996) The corticotropin-releasing factor (CRF) hypothesis of depression: new findings and new directions. Mol Psychiatry 1(4):336–342

Oei NY, Everaerd WT, Elzinga BM, van Well S, Bermond B (2006) Psychosocial stress impairs working memory at high loads: an association with cortisol levels and memory retrieval. Stress 9 (3):133–141

Oei NY, Tollenaar MS, Spinhoven P, Elzinga BM (2009) Hydrocortisone reduces emotional distracter interference in working memory. Psychoneuroendocrinology 34(9):1284–1293

Pariante CM, Lightman SL (2008) The HPA axis in major depression: classical theories and new developments. Trends Neurosci 31 (9):464–468

Pariante CM, Thomas SA, Lovestone S, Makoff A, Kerwin RW (2004) Do antidepressants regulate how cortisol affects the brain? Psychoneuroendocrinology 29(4):423–447

Parker KJ, Schatzberg AF, Lyons DM (2003) Neuroendocrine aspects of hypercortisolism in major depression. Horm Behav 43(1):60–66

Plotsky PM, Owens MJ, Nemeroff CB (1998) Psychoneuroendocrinology of depression. Hypothalamic-pituitary-adrenal axis. Psychiatr Clin North Am 21(2):293–307

Porter RJ, Barnett NA, Idey A, McGuckin EA, O'Brien JT (2002) Effects of hydrocortisone administration on cognitive function in the elderly. J Psychopharmacol 16(1):65–71

Quraishi S, Walshe M, McDonald C, Schulze K, Kravariti E, Bramon E et al (2009) Memory functioning in familial bipolar I disorder patients and their relatives. Bipolar Disord 11 (2):209–214

Robinson SJ, Sunram-Lea SI, Leach J, Owen-Lynch PJ (2008) The effects of exposure to an acute naturalistic stressor on working memory, state anxiety and salivary cortisol concentrations. Stress 11(2):115–124

Rohleder N, Wolf JM, Wolf OT (2010) Glucocorticoid sensitivity of cognitive and inflammatory processes in depression and post-traumatic stress disorder. Neurosci Biobehav Rev 35(1):104–114

Roozendaal B, McReynolds JR, McGaugh JL (2004) The basolateral amygdala interacts with the medial prefrontal cortex in regulating glucocorticoid effects on working memory impairment. J Neurosci 24(6):1385–1392

Roozendaal B, Hui GK, Hui IR, Berlau DJ, McGaugh JL, Weinberger NM (2006a) Basolateral amygdala noradrenergic activity mediates corticosterone-induced enhancement of auditory fear conditioning. Neurobiol Learn Mem 86(3):249–255

Roozendaal B, Okuda S, de Quervain DJ, McGaugh JL (2006b) Glucocorticoids interact with emotion-induced noradrenergic activation in influencing different memory functions. Neuroscience 138 (3):901–910

Schlosser N, Wolf OT, Fernando SC, Riedesel K, Otte C, Muhtz C et al (2010) Effects of acute cortisol administration on autobiographical memory in patients with major depression and healthy controls. Psychoneuroendocrinology 35(2):316–320

Schoofs D, Preuss D, Wolf OT (2008) Psychosocial stress induces working memory impairments in an n-back paradigm. Psychoneuroendocrinology 33(5):643–653

Schoofs D, Wolf OT, Smeets T (2009) Cold pressor stress impairs performance on working memory tasks requiring executive functions in healthy young men. Behav Neurosci 123(5):1066–1075

Schule C, Baghai TC, Eser D, Rupprecht R (2009) Hypothalamic-pituitary-adrenocortical system dysregulation and new treatment strategies in depression. Expert Rev Neurother 9 (7):1005–1019

Shansky RM, Rubinow K, Brennan A, Arnsten AF (2006) The effects of sex and hormonal status on restraint-stress-induced working memory impairment. Behav Brain Funct 2:8

Smeets T, Jelicic M, Merckelbach H (2006) The effect of acute stress on memory depends on word valence. Int J Psychophysiol 62(1):30–37

Squire LR (1992) Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychol Rev 99 (2):195–231

Terfehr K, Wolf OT, Schlosser N, Carvalho Fernando S, Otte C, Muhtz C et al (in press) Cortisol administration and memory in major depression. J Clin Psychiatry (in press)

Thomson F, Craighead M (2008) Innovative approaches for the treatment of depression: targeting the HPA axis. Neurochem Res 33(4):691–707

Van Den Eede F, Van den Bossche B, Hulstijn W, Sabbe BG, Cosyns P, Claes SJ (2006) Combined dexamethasone/CRF test in remitted outpatients with recurrent major depressive disorder. J Affect Disord 93(1–3):259–263

Veiel HO (1997) A preliminary profile of neuropsychological deficits associated with major depression. J Clin Exp Neuropsychol 19 (4):587–603

Webster MJ, Knable MB, O'Grady J, Orthmann J, Weickert CS (2002) Regional specificity of brain glucocorticoid receptor mRNA alterations in subjects with schizophrenia and mood disorders. Mol Psychiatry 7(9):985–994, 924

Wechsler D (1987) Wechsler memory scale-revised manual. Psychological Corporation, San Antonio

Wittchen HU, Zaudig M, Fydrich T (1997) Strukturiertes Klinisches Interview für DSM-IV. Achse I: Psychische Störungen. SKID-I.: Hogrefe. Göttingen, Bern, Toronto, Seattle

Wolf OT, Convit A, McHugh PF, Kandil E, Thorn EL, De Santi S et al (2001) Cortisol differentially affects memory in young and elderly men. Behav Neurosci 115(5):1002–1011

Young AH, Sahakian BJ, Robbins TW, Cowen PJ (1999) The effects of chronic administration of hydrocortisone on cognitive function in normal male volunteers. Psychopharmacology (Berl) 145 (3):260–266

Young AH, Gallagher P, Watson S, Del-Estal D, Owen BM, Ferrier IN (2004) Improvements in neurocognitive function and mood following adjunctive treatment with mifepristone (RU-486) in bipolar disorder. Neuropsychopharmacology 29(8):1538–1545