Effects of Acute Hydrocortisone Administration on Declarative Memory in Patients With Major Depressive Disorder: A Placebo-Controlled, Double-Blind Crossover Study

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ABSTRACT

Objective: Major depressive disorder (MDD) has been associated with hypercortisolism, reduced glucocorticoid feedback sensitivity, and impaired memory function. In healthy subjects, administration of hydrocortisone impairs declarative memory. The aim of this study was to examine the effects of acute hydrocortisone administration on memory retrieval in MDD patients and healthy controls. We further tested whether the enhancing or impairing effects of hydrocortisone would prevail when it was given after encoding and when delayed retrieval was tested at a time point when glucocorticoid levels were still elevated.

Method: In a placebo-controlled, double-blind crossover study, 44 patients with *DSM-IV* MDD and 51 healthy control participants received either placebo or 10 mg of hydrocortisone orally before memory testing. A word list paradigm and the Logical Memory Test from the Wechsler Memory Scale were applied. The study was conducted from April 2008 until April 2010 at sites in Bielefeld and Hamburg, Germany.

Results: In both memory tests, patients with MDD performed worse than controls. Healthy controls showed impaired memory performance after hydrocortisone administration compared to placebo. In contrast, hydrocortisone had no effects on memory in MDD patients. Furthermore, in healthy controls we found that administration of hydrocortisone immediately after learning did not lead to an enhanced free recall during increased cortisol levels.

Conclusions: It appears that the impairing effects of hydrocortisone on memory performance are missing in patients with MDD. This might be interpreted in the context of reduced central glucocorticoid receptor functioning.

J Clin Psychiatry 2011;72(12):1644–1650

Submitted: *May 12, 2010; accepted July 30, 2010.*
Online ahead of print: *April 19, 2011 (doi:10.4088/JCP.10m06240).*

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Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, as evidenced by, among other conditions, enhanced basal and stimulated cortisol release as well as high cortisol levels after dexamethasone administration, is a prominent finding in major depressive disorder (MDD).[1–4] Cortisol acts via binding to mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs). These receptors show a high density in the hippocampus[5] and the prefrontal cortex,[6] which are closely related to cognitive functions. Interestingly, in these brain regions reduced GR messenger RNA,[7] as well as an increased methylation of the GR promoter inhibiting GR expression,[8] has been found for depressive patients. Further research suggests GR gene polymorphisms to be associated with depression.[9,10]

In healthy subjects, previous investigations using word lists, paired associates, or autobiographical cues found that acute administration of glucocorticoids impairs memory retrieval.[11–15] The same evidence comes from rat studies, indicating that glucocorticoids influence cognitive performance.[16,17] Moreover, psychosocial stress-induced cortisol elevations lead to poorer memory retrieval.[18–21]

In contrast to the impairing effects of glucocorticoids on memory retrieval, a vast literature on rodent studies,[22–24] as well as studies in healthy subjects[25–28] has illustrated that glucocorticoids enhance memory consolidation. Even though the findings are not completely consistent, it has been observed that prelearning glucocorticoid treatment[27,29] or immediate postlearning stress[28,30] enhanced memory consolidation, resulting in better memory retrieval days or weeks later.

Cognitive deficits are frequent in MDD.[31] One of the best-investigated cognitive functions in depression is the hippocampal-based episodic declarative memory, suggesting an impairment in MDD patients,[31–33] although not all studies agree.[34–36]

Surprisingly, only a few studies have investigated the association between HPA axis functioning and memory performance in depression.[34,37–43] Some studies have found an association between cortisol levels and cognitive impairment in depressed patients[30,37,39,40,42,44] or predominantly in depressed patients with psychotic symptoms,[38] while other studies failed to replicate these findings.[41,43,45–47] However, the cross-sectional and correlational design of these studies limits the ability to draw causal conclusions.

To the best of our knowledge, the only study that has investigated the effect of glucocorticoid administration on declarative memory performance until now was done by Bremner et al.[48] They found that, after 2 days of 2-mg dexamethasone treatment, memory performance was improved in patients with MDD. The authors suggested that a reduction of cortisol after dexamethasone treatment might have led to the observed memory improvement. In a recently published study by our group, we investigated the effect of acute hydrocortisone administration on autobiographic memory and found reduced memory specificity in healthy subjects after hydrocortisone intake, while the administration of hydrocortisone in patients with MDD did not further reduce autobiographical memory retrieval.[49] However, the autobiographical memory test predominantly measures the quality of memory

Clinical Points

- A significant percentage of patients with MDD show hypothalamic-pituitary-adrenal axis (HPA) dysregulations, for example, hypercortisolism or reduced glucocorticoid receptor function.
- The results of our study further strengthened the hypothesis of reduced central glucocorticoid receptor functioning in MDD.
- The corticosteroid receptor hypothesis of depression has stimulated pharmacologic research to strive for new antidepressant agents that act directly on different sites within the HPA axis.

retrieval but not quantity, whereas the impairing effects of glucocorticoids have been shown more consistently.

No study has investigated the effect of acute hydrocortisone administration on declarative memory performance in MDD until now. Thus, we compared patients with MDD with a healthy control group concerning their declarative memory performance after acute hydrocortisone administration. We hypothesized that healthy control subjects would show impaired declarative memory retrieval following hydrocortisone intake. 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 would show an overall reduced declarative memory performance compared to healthy control subjects. We further tested whether the enhancing or impairing effects of cortisol would prevail when hydrocortisone was given after encoding and when delayed retrieval was tested at a time point when glucocorticoid levels were still elevated.

METHOD

Subjects

Forty-four inpatients with *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, MDD and 51, healthy controls aged 18 years or older participated in our study. They 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, and at Schön Klinik, Hamburg-Eilbek, Germany, from April 2008 until April 2010.

Subjects were excluded if they had any of the following current or previous medical conditions: central nervous system–relevant somatic diseases or severe somatic diseases (eg, neurologic diseases), metabolic diseases (eg, thyroid disease, diabetes), an organic shift in cortisol secretion (eg, Morbus Cushing), immune-mediated diseases, medicated hypertension, severe cardiovascular diseases, or other current infections. Further exclusion criteria were current pregnancy, the use of β-blockers, or anorexia and 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 subjects. Healthy subjects 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 Hamburg.

Procedure

To assess psychiatric diagnoses, subjects were interviewed using the Structured Clinical Interview for *DSM-IV* Axis I and II Disorders. Depressive mood state was measured using the Beck Depression Inventory (BDI).[50]

In this placebo-controlled, double-blind crossover study, each participant was tested twice with parallel versions of a word list paradigm (see below) as well as the Logical Memory Test of the Wechsler Memory Scale.[51] The 2 versions of each test were counterbalanced across the 2 test conditions. The study protocol is presented in Table 1. Before administration of 10 mg hydrocortisone or placebo the participants learned one of the short stories from the Logical Memory Test. Thirty minutes after either hydrocortisone or placebo was administered, the participants were asked to recall the words from the word list they had learned the day before (free recall). About 60 minutes after recalling the word list, the participants had to recall as many content words of the Logical Memory Test as possible. The same procedure with the alternate test condition was repeated after 1 week (see Table 2).

The Logical Memory Test consisted of 2 short stories, each containing 25 content words. The short stories were read aloud by the investigator. The participants were then instructed to memorize as many details as possible. The answers were scored by a trained rater according to the instructions of the Wechsler Memory Scale manual.[52]

The word list paradigm consisted of 21 words. Subjects were asked to memorize as many words as possible in no particular order. Word lists were taken from a study of Kuhlmann et al[18] and were reduced from 30 to 21 words, including 7 neutral, 7 positive, and 7 negative words each. The 2 word lists were comparable in emotionality, usage, and length.

Momentary mood was measured at the beginning and at the end of each testing with the Multidimensional Mood State Questionnaire (MDMQ),[53] which comprises 3 scales: elevated vs depressed mood, wakefulness vs sleepiness, and calmness vs restlessness.

Saliva was collected 10 minutes before (T1) and 45 minutes (T2) and 90 minutes (T3) after hydrocortisone administration, using saliva collection devices (Sarstedt AG, Rommelsdorf, Germany). After being stored at room temperature until the session was completed, the saliva was kept at −80°C until the biochemical analysis. Salivary

Table 1. Experimental Protocol Indicating Time of Cognitive Testing and Saliva Sampling

Day	Time, h	Procedure
1	1530	Word list learning and immediate recall
2	1530	Saliva collection
2	1535	Logical Memory Test (learning phase)
2	1540	Administration of hydrocortisone or placebo
2	1625	Saliva collection + word list (delayed recall)
2	1710	Logical Memory Test (delayed recall) + saliva collection

cortisol levels were measured using a commercial radioimmunoassay (DRG International, Inc, Marburg, Germany). Interassay and intraassay coefficients of variation were below 8%. All biochemical analyses were done by the Department of Biologic Psychiatry, University Medical Center Hamburg-Eppendorf, Germany.

Statistical Analysis

Statistical analyses were performed using SPSS version 15.0 (IBM, Chicago, Illinois). Demographic data were analyzed using the Pearson χ^2 test for categorical data and the Student *t* test for continuous data.

Effects of hydrocortisone on declarative memory performance as well as salivary cortisol were analyzed using analysis of variance (ANOVA) or analysis of covariance (ANCOVA) with repeated measurements. Bonferroni-adjusted post hoc analyses were used in case of a significant group effect.

RESULTS

Demographic and Clinical Data

Patients with MDD and control participants did not differ concerning sociodemographic variables (Table 2). Results of the MDMQ are also presented in Table 2. Eleven patients had a current comorbid diagnosis of anxiety disorder. Thirty-one patients were treated with antidepressant medication (selective serotonin norepinephrine reuptake inhibitor, n = 12; serotonin norepinephrine reuptake inhibitor, n = 1; selective serotonin reuptake inhibitor, n = 18). All healthy subjects were free of medication.

Cortisol Levels

Cortisol measurements were conducted for 21 MDD patients and 27 healthy controls. A 2 × 3 × 2 ANOVA was performed with condition, time, and group as main factors.

A significant condition effect was revealed, reflecting increased saliva cortisol levels after administration of hydrocortisone compared to placebo ($F_{1,46} = 86.54$, $P < .001$). Furthermore, there was a significant time effect ($F_{1,46} = 60.45$, $P < .001$) as well as a significant condition-by-time interaction effect ($F_{2,92} = 64.39$, $P < .001$). In the hydrocortisone condition, all post hoc *t* tests were significant (all *P* values < .001). Cortisol levels at baseline did not differ between the 2 conditions ($t_{50} = 1.01$, NS). There was a trend toward a group effect ($F_{1,46} = 3.90$, $P = .054$) as well as a significant group-by-condition interaction ($F_{1,46} = 4.10$, $P = .049$) showing a slightly higher cortisol increase in patients with MDD after hydrocortisone administration (Figure 1). However, post hoc tests did not find any significant difference between patients and controls at each measurement point in the hydrocortisone or in the placebo condition.

Declarative Memory Test

Word list paradigm. To analyze the effects of hydrocortisone on declarative memory (word list paradigm) a 2 × 2 ANOVA with repeated measures was conducted with the main factors *group* and *condition*. Percentage of correctly recalled words relative to the words recalled after the fifth learning trial on the day before served as dependent variable. There was no significant effect of the main factor *group* ($F_{1,93} = 1.33$, NS). The main effect of *condition* marginally failed to reach significance ($F_{1,93} = 3.09$, $P = .082$). However, ANOVA indicated a significant *condition*-by-*group* interaction ($F_{1,93} = 4.12$, $P = .045$). Post hoc analyses revealed that, after hydrocortisone administration, memory retrieval was significantly impaired in the control group ($t_{50} = -2.81$, $P = .007$) but not in the MDD group ($t_{43} = 0.18$, $P = .856$, NS).

In the placebo condition, depressed patients showed a significantly poorer retrieval performance compared to control subjects ($t_{93} = -2.29$, $P = .024$; Figure 2). The increase of cortisol after hydrocortisone treatment did not influence the results of the cognitive data when introduced into the analyses as covariate ($P > .34$).

Regarding valence of the words, no significant effect (main effects as well as interactions) could be found. Therefore, we abandoned more precise illustrations on valence analyses.

Checking for condition order effects, we detected a significantly poorer performance in the second test session compared to the first test session ($F_{1,93} = 24.76$, $P < .001$). Against this background, we controlled the analyses for *condition order* and found again a significant *condition*-by-*group* interaction effect (ANCOVA: $F_{1,93} = 5.91$, $P = .017$). In this analysis, the main effect for *group* stayed nonsignificant ($F_{1,92} = 1.24$, $P = .269$, NS), while the *condition* effect reached significance ($F_{1,93} = 21.81$, $P < .001$).

To control for potential effects of hydrocortisone intake on mood, we added the change of each MDMQ scale separately into the analyses. However, no significant effects of these covariates were revealed.

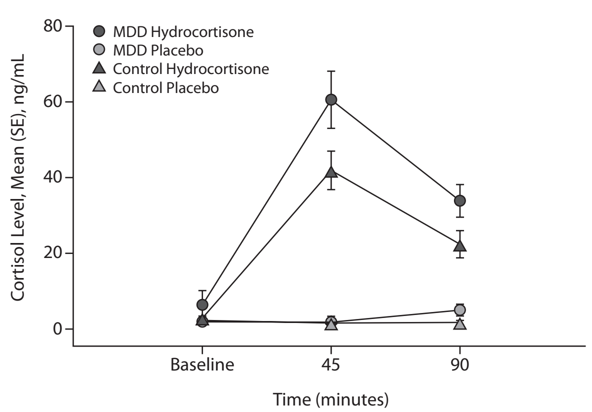
Logical Memory Test. We performed a 2 × 2 ANCOVA with repeated measures and total number of recalled content words as dependent variables. *Condition order* was entered as covariate. No main effect was found for *group* ($F_{1,91} = 1.16$, NS), while the main effect for *condition* marginally failed to reach significance ($F_{1,91} = 3.20$, $P = .077$). Results indicate a significant interaction between *condition* and *group* ($F_{1,91} = 4.09$, $P = .046$) (Table 3). Similar to the results of the word list paradigm, post hoc testing revealed a trend to a poorer performance in the Logical Memory Test after hydrocortisone administration compared to the placebo condition in healthy controls ($t_{50} = -1{,}95$, $P = .057$), while

Table 2. Sociodemographic and Clinical Characteristics of Subjects With Major Depressive Disorder (n = 44) and Healthy Controls (n = 51) Administered Hydrocortisone or Placebo

			Statistics		Analysis of Variance					
Characteristic	MDD (n = 44)	Controls (n = 51)	t or χ^2	P	Time	Treatment	Group	Time × Group	Treatment × Group	Treatment × Time
Age, mean (SD), y	34.32 (9.64)	32.67 (10.13)	$t = 0.81$	.420, NS						
Sex, female, %	61.36	58.82	$\chi^2 = 0.64$	.801, NS						
Formal education, mean (SD), y	11.11 (1.48)	11.57 (1.50)	$t = -1.48$	.142, NS						
BDI total score, mean (SD)	23.38 (10.52)	3.02 (3.77)	$t = 12.45$	< .001						
MDMQ: elevated vs depressed mood item score, mean (SD)					$P < .001$	NS	$P = .001$	$P = .034$	NS	NS
Placebo										
Before testing	13.7 (3.4)	16.8 (1.9)								
After testing	11.8 (1.9)	13.3 (1.4)								
Hydrocortisone:										
Before testing	13.7 (3.5)	17.1 (1.9)								
After testing	11.6 (1.8)	13.2 (1.9)								
MDMQ: wakefulness vs sleepiness item score, mean (SD)					$P < .001$	NS	$P = .001$	$P = .001$	NS	NS
Placebo										
Before testing	12.2 (3.8)	13.2 (3.1)								
After testing	11.7 (1.6)	11.8 (1.2)								
Hydrocortisone:										
Before testing	12.1 (3.6)	14.4 (2.8)								
After testing	11.5 (1.2)	11.9 (1.6)								
MDMQ: calmness vs restlessness item score, mean (SD)					$P < .001$	NS	NS	$P = .001$	NS	NS
Placebo										
Before testing	12.8 (3.8)	15.1 (2.1)								
After testing	11.7 (2.4)	9.9 (1.5)								
Hydrocortisone:										
Before testing	12.8 (2.9)	15.9 (2.2)								
After testing	11.9 (1.6)	10.1 (1.4)								

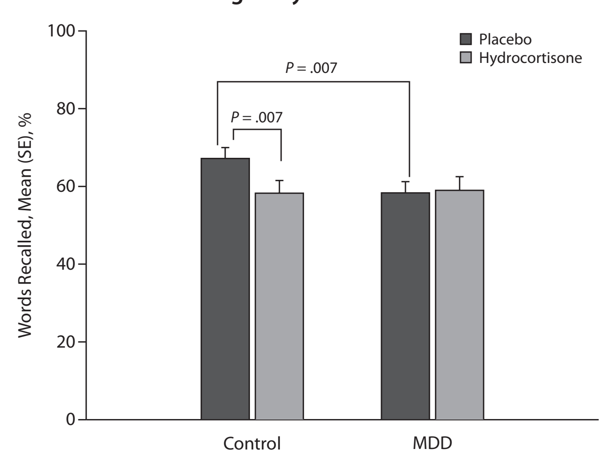
Abbreviations: BDI = Beck Depression Inventory, MDMQ = Multidimensional Mood State Questionnaire (a German multidimensional mood state questionnaire), NS = not significant.

Figure 1. Saliva Cortisol Levels in Patients With MDD (n = 21) and Healthy Control Subjects (n = 27) After Placebo and Hydrocortisone Administration[a]



[a]Analysis of variance revealed that cortisol levels were higher after 10 mg of hydrocortisone compared to placebo, with MDD patients showing a slightly stronger increase in cortisol in the hydrocortisone condition, as indicated by a significant group-by-condition interaction effect.
Abbreviation: MDD = major depressive disorder.

Figure 2. Percentage of Words Retrieved in the Word List Paradigm in Relation to the Last Learning List on the Previous Day in Patients with MDD (n = 44) and Healthy Control Subjects (n = 51) After Placebo and After Administration of 10 mg of Hydrocortisone[a]



[a]A significant condition-by-group interaction effect was found, with MDD patients showing a worse memory performance compared to the control group. Healthy controls, in contrast to MDD patients, had impaired memory retrieval after hydrocortisone compared to placebo.
Abbreviation: MDD = major depressive disorder.

Table 3. Mean (SD) Number of Content Words Recalled in the Logical Memory Test (maximum score = 25) in Patients With MDD (n = 43) and Healthy Control Subjects (n = 51) After Placebo and Hydrocortisone Administration

	Controls (n = 51)	Depression (n = 43)	Statistics
Placebo	14.75 (4.20)	13.05 (4.31)	$t = -1.93$, $P = .057$, NS
Hydrocortisone	13.63 (4.73)	13.63 (4.23)	$t = 0.00$, $P = 1.00$, NS

Abbreviations: MDD = major depressive disorder, NS = not significant.

MDD patients showed no further memory impairment after hydrocortisone ($t_{42} = 0.865$, NS).

DISCUSSION

To the best of our knowledge, this is the first study investigating the effects of acute hydrocortisone administration on declarative memory performance in patients with MDD and healthy controls. We found that the impairing effects of hydrocortisone on memory in MDD patients were absent, whereas in healthy controls hydrocortisone administration impaired the recall of words. The impairing effects of hydrocortisone or stress treatment on memory retrieval have been demonstrated repeatedly. For example, Wolf et al[12] showed that hydrocortisone administration impairs the recall of a word list learned before. This is in line with our results and those of other studies in which recall of material learned 24 hours earlier was impaired when glucocorticoids were given before delayed recall testing.[14,20] In addition, our results agree with those of studies in which impaired memory observed after stress-induced cortisol elevations.[18,19,21]

When testing whether the enhancing or the impairing influences of cortisol would prevail if hydrocortisone were given after encoding and delayed retrieval were tested at a time point when glucocorticoid levels were still elevated, we found effects that were similar to those in the word list paradigm: in healthy controls, hydrocortisone administration had no enhancing but impairing effects on memory performance. These results suggest that hydrocortisone had stronger effects on retrieval compared to consolidation. When investigating the effects of glucocorticoid on memory consolidation, an enhancing effect of hydrocortisone administration has been found in some[25,29] but not all studies.[14] As mentioned above, a crucial difference of our experiment compared to other studies[25,27,30,54] is that glucocorticoid levels remained elevated at the time of retention testing. Possibly, enhancing consolidation effects are only detectable when cortisol levels have returned to baseline at the time of retrieval testing.

Depressive patients exhibited impaired memory retrieval compared to healthy controls in the placebo condition, but after hydrocortisone administration memory performance was comparable in both groups. Thus, the administration of hydrocortisone did not further reduce memory retrieval in MDD patients. This is in line with one of our earlier studies[49] examining cortisol effects on the specificity of autobiographical memory retrieval. While after hydrocortisone intake, healthy subjects reported significantly fewer specific memories compared to the placebo condition, memory specificity of MDD patients was not affected by hydrocortisone.

The missing impairing glucocorticoid effects in MDD patients might be discussed in the context of reduced GR sensitivity in MDD.[55] Investigations using the dexamethasone suppression test and the combined dexamethasone/corticotropin-releasing factor test in MDD showed a reduced feedback sensitivity in GR, which has been interpreted as reflecting an increased central corticotropin-releasing hormone drive[56] and/or reduction of GR functioning.[57] Other authors have demonstrated that GR signaling is reduced in depression, suggesting that the brain is in a state of glucocorticoid resistance.[58] As described above, GRs exhibit a high density in the hippocampus,[59] which is important for successful memory retrieval.[60–64] Especially in this brain region, reduced GR messenger RNA has been found in MDD patients,[7] which can also result in a diminished effect of glucocorticoids on memory function. Interestingly, positron emission tomography studies[65,66] as well as a first functional magnetic resonance imaging study[67] suggest that hydrocortisone treatment leads to a reduced activation in both hippocampi during memory retrieval. When cortisol levels are high, glucocorticoids mostly act via GRs, which have a much lower affinity for cortisol than MRs. Nevertheless, effects mediated by MRs, which are already occupied to a great extent under basal conditions, cannot be ruled out.[68] Interestingly, animal studies have shown that elevated cortisol down-regulates both GRs and MRs.[59] In sum, the lack of an effect of acute hydrocortisone administration on memory retrieval might be due to reduced functioning of hippocampal GRs and MRs, while it is currently not possible to exactly disentangle the different effects of GRs and MRs on memory.

Another study has investigated the effects of dexamethasone on declarative memory in MDD.[48] In contrast to our study, the dexamethasone study found memory performance to be improved in MDD after dexamethasone. The authors suggest that a reduction of cortisol after dexamethasone might have led to the observed memory improvement. However, the chosen glucocorticoid (dexamethasone vs hydrocortisone) and study design (repeated glucocorticoid treatment vs single treatment) makes it difficult to compare this study with ours.

Some limitations of the study should be mentioned. A weakness is that a more thorough evaluation of the HPA axis activity/reactivity (ie, day profile, feedback sensitivity) was not available. Therefore we cannot conclude that the observed effects are merely the result of reduced GR sensitivity but might possibly be due to saturated GR occupancy resulting from hypercortisolism. For example, Hinkelmann et al[37] stated that, compared to healthy controls, MDD patients had higher cortisol levels that were correlated with poorer memory performance. However, in our study cortisol levels before testing did not differ between patients and controls, suggesting comparable cortisol release in the afternoon. In addition, many patients in our study were medicated, which might have influenced HPA-axis functioning, glucocorticoid sensitivity, and memory performance.[58] Therefore, it would be interesting to test the effects of hydrocortisone on declarative memory performance in a sample of medication-free MDD patients in the future. To investigate the effect of cortisol on memory consolidation, an experiment with a retention interval of 24 hours[27,29,30] should be conducted. Furthermore, it would be interesting to include nonverbal memory measurements in future research. As animal studies have clearly demonstrated that enhancement of memory consolidation by glucocorticoids critically depends on coactivation of peripheral and/or central adrenergic mechanisms,[69,70] an experiment with more arousing learning conditions than in the present study could be indicated. This is also underlined by a study of Kuhlmann and Wolf,[27] in which the authors found a stronger enhancing effect on consolidation for emotionally arousing material. Moreover, other factors such as deficits in executive control, which are related to declarative memory performance, may also be influenced by cortisol.[37] Concerning the lack of cortisol effect on memory performance in MDD, a floor effect cannot be fully excluded, but it appears unlikely, since MDD patients were able to recall almost 60% of the words they had learned on the previous day.

In summary, the present study shows a lack of an effect of hydrocortisone on quantitative memory performance in MDD. One possible explanation might be a reduced glucocorticoid receptor sensitivity in patients with MDD. Given the limitations of our study discussed above, further studies should extend the study design using a multidimensional and multimethodological assessment of glucocorticoid receptor sensitivity.

Drug names: dexamethasone (Ozurdex, Maxidex, and others), hydrocortisone (Synacort, Ala-Cort, and others).

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Funding/support: This study was supported by a grant from the Deutsche Forschungsgemeinschaft (WI 3396/1-1) awarded to Drs Wolf, Driessen, and Wingenfeld.

Potential conflicts of interest: The authors report no additional financial or other relationship relevant to the subject of this article.

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