

Provided for non-commercial research and education use.
Not for reproduction, distribution or commercial use.

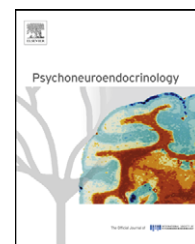


This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

<http://www.elsevier.com/copyright>

available at www.sciencedirect.comjournal homepage: www.elsevier.com/locate/psyneuen

SHORT COMMUNICATION

Effects of acute cortisol administration on autobiographical memory in patients with major depression and healthy controls

Nicole Schlosser^a, Oliver Tobias Wolf^b, Silvia Carvalho Fernando^a,
Kirsten Riedesel^c, Christian Otte^d, Christoph Muhtz^d, Thomas Beblo^a,
Martin Driessen^{a,e}, Bernd Löwe^c, Katja Wingenfeld^{c,*}

^a Department of Psychiatry and Psychotherapy Bethel, Ev. Hospital Bielefeld, Bielefeld, Germany

^b Department of Cognitive Psychology, University of Bochum, Bochum, Germany

^c Department of Psychosomatic Medicine and Psychotherapy, University Medical Center Hamburg-Eppendorf, Martinistr. 52, Hamburg 20246, Germany

^d Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

^e Luebeck School of Medicine, Luebeck, Germany

Received 30 March 2009; received in revised form 23 June 2009; accepted 23 June 2009

KEYWORDS

Depression;
Autobiographical
memory;
Cortisol;
HPA-axis;
Hippocampus;
Human

Summary

Objective: Overgeneral autobiographical memory has become a well established phenomenon within major depressive disorder (MDD). Neuroendocrinologically, MDD is often characterized by a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, i.e. hypercortisolemia and reduced feedback sensitivity. In healthy participants cortisol administration has been found to impair autobiographical memory retrieval. The purpose of this study was to compare the effects of acute cortisol administration on autobiographical memory in MDD patients with the effects observed in healthy controls. We hypothesized that in contrast to healthy control subjects acute cortisol administration would not affect autobiographical memory performance in MDD due to reduced central glucocorticoid sensitivity.

Methods: In a placebo-controlled, double-blind crossover study, 16 patients with MDD and 16 healthy control subjects received a placebo or 10 mg of hydrocortisone orally before autobiographical memory testing (AMT).

Results: In the placebo condition depressed patients performed poorer than controls. After hydrocortisone intake, healthy subjects reported significantly fewer specific memories on the AMT compared to placebo treatment. In contrast, memory specificity of MDD patients was not affected by hydrocortisone treatment.

* Corresponding author. Tel.: +49 40 42 80 3 41 69; fax: +49 40 42 80 3 49 75.
E-mail address: k.wingenfeld@uke.uni-hamburg.de (K. Wingenfeld).

Conclusions: The present findings replicate previous findings of impaired autobiographical memory retrieval after hydrocortisone treatment in healthy subjects and of impaired AMT performance in depressed patients. We speculate that the missing acute impairing effect of hydrocortisone on autobiographical memory in depressed patients might reflect reduced central glucocorticoid sensitivity. However alternative explanations cannot be ruled out.

© 2009 Elsevier Ltd. All rights reserved.

1. Introduction

Patients with major depressive disorder (MDD) often display disturbances in recalling specific events of their past (Van Vreeswijk and De Wilde, 2004; Williams et al., 2007) and are instead prone to reporting recurring events at a more general level. Beside psychological theories explaining 'overgeneral memory', neuroendocrine research proposes additional explanations for reduced autobiographical memory specificity in depression. Previous investigations have found that acute administration of glucocorticoids (GC) impair memory retrieval in healthy human subjects (Wolf, 2008). Though studies have focused primarily on episodic memory (e.g. word lists), an initial study by Buss et al. (2004) replicated the impairing effects of GC on autobiographical memory. In their study, healthy students generated fewer specific autobiographical memories after cortisol administration compared to a placebo. The authors hypothesized that autobiographical memory deficits in depression might result from cortisol hypersecretion, a repeatedly observed neuroendocrine characteristic of depressive disorder (Barden, 2004; Parker et al., 2003). Moreover, MDD seems to be characterized by altered glucocorticoid receptor (GR) functioning (Holsboer, 2000; Webster et al., 2002), i.e. a reduced responsiveness to circulating GCs. Studies in which basal cortisol levels of MDD patients have been correlated with their memory performance (Egeland et al., 2005; Gomez et al., 2006) found a negative association between basal cortisol levels and semantic memory performance. The only study examining the effect of basal cortisol level on autobiographical memory in MDD patients (Barnhofer et al., 2005) found no association. To our knowledge, no study has investigated the relation between acute cortisol elevation and memory performance in MDD by now. The purpose of the present study was to examine the impact of acute cortisol administration on autobiographical memory performance in patients with MDD compared to healthy control subjects. We hypothesized first that healthy control subjects show an impaired autobiographical memory retrieval 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 autobiographical memory performance compared to healthy control subjects.

2. Methods and material

Sixteen inpatients with MDD (8 females, 8 males) and sixteen age and gender matched healthy control subjects (8 females, 8 males) participated in our double-blind, placebo-controlled, crossover study. Psychiatric diagnosis was made

using the Structured Clinical Interview for DSM-IV, SCID-I for Axis-I disorders (Wittchen et al., 1997). Severity of depressive symptoms was assessed by means of the Beck Depression Inventory (BDI, Beck and Steer, 1994). Control subjects were recruited by local advertising. Inclusion criterion for patients was a current diagnosis of MDD. Exclusion criteria for all subjects were any physically derived hormone diseases (e.g. thyroid disease, diabetes, etc.).

All procedures were carried out with adequate understanding of the subjects. Written informed consent was obtained from all subjects. The study was approved by the University of Muenster Ethics Committee and is in accordance with the Declaration of Helsinki.

Each participant was tested twice with parallel versions of the autobiographical memory cueing test (AMT, see below), with the two versions being counterbalanced across the two treatment conditions (test–retest interval 5–7 days). A dosage of 10 mg of hydrocortisone (Jenapharm®) or a placebo was administered orally 1 h prior to memory testing, which took place between 1600 h and 1800 h.

A modified version of the AMT (Buss et al., 2004; Williams and Broadbent, 1986) was used. After an initial practice on one cue word, the participants were instructed to write down a specific event from their past in response to two positive, negative and neutral adjectives (see Appendix) which were consecutively presented on cards. Subjects were instructed to recall events that had happened at least 1 day prior to testing that had taken place at a certain time and place and did not last any longer than 1 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. 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 (see also Appendix 2). Each specific answer was given a score of 1 and non-specific answers a score of 0. A high inter-rater reliability was attained ($Kappa = .95$).

Effects of hydrocortisone on autobiographical memory performance were analyzed using a 3 (valence: positive, negative, neutral) \times 2 (treatment: cortisol vs. placebo) \times 2 (group: patients vs. controls) factorial analysis of variance (ANOVA) with repeated measures. Bonferroni adjusted post hoc tests were used.

3. Results

3.1. Demographic and clinical data

The mean age of the patients (34.88 years [SD = 7.22]) did not differ from control subjects (33.31 years [SD = 7.30], $t_{(30)} = .609$, n.s.). The mean length of education was longer

Table 1 Means (and standard deviations) of specific memories in patients with MDD ($n = 16$) and healthy control subjects ($n = 16$) after placebo and hydrocortisone treatment.

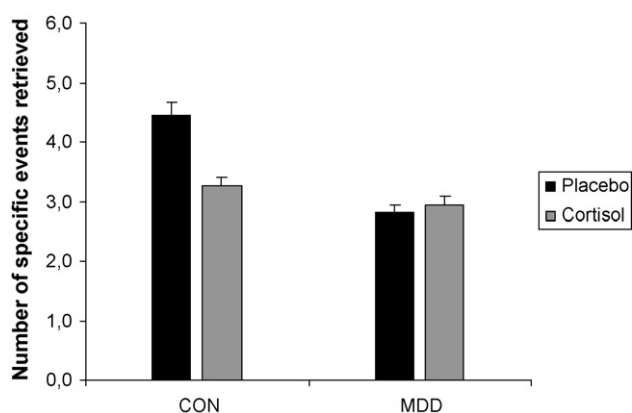
	Placebo		Hydrocortisone	
	MDD	Controls	MDD	Controls
Total	2.81 (1.68)	4.44 (1.63)	2.94 (1.39)	3.25 (1.69)
Positive cues	.75 (.68)	1.56 (.63)	1.06 (.77)	1.25 (.77)
Negative cues	1.19 (.75)	1.44 (.63)	.88 (.81)	1.06 (.85)
Neutral cues	.88 (.96)	1.44 (.73)	1.00 (.63)	.94 (.77)

in the control than the patients group [11.88 (1.36) years vs. 10.75 (1.07); $t_{(30)} = -2.61$, $p < .001$]. As expected, patients were more depressed than control subjects according to the BDI [23.40 (8.17) vs. 2.63 (3.52); $t_{(30)} = 9.09$, $p < .001$]. MDD patients reported a median of 3 prior episodes of depression with a mean length of the current episode of 28 weeks. All patients were treated with antidepressant medication (SSNRI $N = 9$, SNRI $N = 1$, SSRI $N = 6$). All healthy subjects were medication free.

3.2. Autobiographical memory test

First, we checked for version effects and found no significant difference in performance between the two AMT versions ($t_{32} = -.21$, $p = .835$, n.s.). We also could not detect an effect of treatment order (ANOVA: effect of treatment $F_{1,30} = 3.22$, $p = .083$; effect of treatment order $F_{1,30} = .75$, n.s.).

With regard to the number of specific memories, ANOVA indicated a significant treatment by group interaction ($F_{1,30} = 5.89$, $p = .021$). Post hoc analyses revealed that following hydrocortisone administration AMT retrieval performance was significantly impaired in the control group – as indicated by fewer specific memories compared to the placebo condition ($t_{15} = -2.82$, $p = .013$) – but not in the MDD group (see Fig. 1). In the hydrocortisone treatment condition, the number of specific answers was comparable for patients and control subjects, whereas under placebo, depressed patients showed a significantly poorer AMT performance compared to control subjects ($t_{30} = -2.77$, $p = .009$).

**Figure 1** Mean number of specific memories in patients with MDD ($n = 16$) and healthy control subjects ($n = 16$) after placebo and hydrocortisone treatment.

Main effects for treatment ($F_{1,30} = 3.86$, $p = .059$) and group ($F_{1,30} = 3.78$, $p = .061$) marginally failed to reach statistical significance. Regarding valence of the word cues, no significant effect (main effect as well as interactions) could be found. Mean scores of autobiographical memory performance are shown in Table 1.

When controlling the analyses for years of education (ANCOVA), we did not find a significant effect of this covariate ($F_{1,29} = .007$, n.s.). While there was a significant treatment by group interaction effect ($F_{1,29} = 6.33$, $p = .018$) in this analyses, only a trend towards a main effect for group ($F_{1,29} = 4.26$, $p = .089$) and no significant treatment effect could be revealed ($F_{1,29} = .98$, n.s.). When controlling the analyses for gender, the results indicated that 'gender' indeed has a significant effect ($F_{1,29} = 6.34$, $p = .018$), while the interaction effect between group and treatment remained stable ($F_{1,29} = 5.82$, $p = .022$). Overall, women showed a better memory performance.

4. Discussion

This is the first study investigating the effect of acute cortisol administration on autobiographical memory in patients with MDD compared to healthy controls. First, we could replicate the finding of autobiographical memory impairment after cortisol administration in healthy subjects (Buss et al., 2004). As expected, depressive patients exhibited impaired autobiographical memory performance compared to healthy control in the placebo condition (Van Vreeswijk and De Wilde, 2004; Williams et al., 2007). Interestingly, after cortisol administration memory performance was comparable in both groups. In patients with MDD, the administration of cortisol did not further reduce autobiographical memory performance as seen in the control group.

These findings are in line with the hypothesis of reduced GR sensitivity in MDD. A prominent finding in MDD is a reduced feedback sensitivity in the dexamethasone suppression test, which has been interpreted as reflecting an exaggerated CRH drive (Nemeroff, 1996) and/or a reduction of functioning of GR (Holsboer, 2000). GRs are known to be important in the regulation of the HPA-axis, especially when endogenous levels of cortisol are high (De Kloet et al., 1998). Furthermore, reduced GR mRNA has been found in several brain regions such as the hippocampus and prefrontal cortex of MDD patients (Webster et al., 2002). Thus, the lack of an effect of acute cortisol administration on memory performance might be due to reduced functioning of hippocampal and/or prefrontal GR. Accordingly, decreased central GC sensitivity in MDD might underlie the results obtained in the present study. One study that has investigated the effects

of dexamethasone (DEX) on declarative memory in MDD, has also hypothesized a lesser effect of GC in patients (Bremner et al., 2004). In contrast to our study, they found memory performance to be improved in MDD patients after DEX. The authors suggest that a reduction of cortisol after DEX might have led to the observed memory improvement. However, the chosen GC (DEX vs. hydrocortisone) and study design (repeated GC treatment vs. single treatment) of the latter study makes a comparison with our current analysis difficult.

Several alternative scenarios could account for the missing effects of acute GC administration on autobiographical memory performance. Overgeneral memory as well as the reduced sensitivity to acute cortisol elevations might be due to hippocampal atrophy which has been consistently found in patients with MDD (Campbell et al., 2004). Cause–effect relationships between hypercortisolemia, hippocampal atrophy and impaired memory retrieval in MDD are still unclear and are discussed with controversy (Wolf, 2008). Alternatively, impaired autobiographical memory performance in MDD patients might be moderated through executive control which is known to be dependent on prefrontal cortex (PFC) function (Dagleish et al., 2007). As the PFC is also occupied with GRs (Lupien and Lepage, 2001), cortisol might not only influence the function of the hippocampus but also the PFC, which might together lead to the observed autobiographical memory impairments. Finally, it has to be acknowledged that cortisol might influence memory performance not directly (via its own receptors), but through more complex interactions with neurotransmitters or neuropeptides (Porter et al., 2004). Recent evidence from patients receiving GC therapy has indicated that their memory retrieval impairments reflect acute rather than chronic GC effects (Coluccia et al., 2008). Thus, it would be interesting to test whether a pharmacological reduction of GC levels in MDD patients would lead to enhanced autobiographical memory performance.

There are several limitations of the study to be mentioned. The main weakness of our study is that data on basal cortisol levels or responses to a dexamethasone suppression test were not available in the present study. Therefore, we cannot explicitly conclude that the observed effects are merely the result of reduced GR sensitivity but possibly also of saturated GR occupancy resulting from hypercortisolemia. Furthermore, all patients in this study were treated with antidepressant medication which could have influenced HPA-axis function, glucocorticoid sensitivity as well as memory performance (Pariante et al., 2004). It would be interesting to test the effects of hydrocortisone on AMT performance in a sample of medication free MDD patients in the future. Deficits in autobiographical memory specificity have been found to be related to a number of different factors including functional avoidance, ruminative tendencies, and deficits in executive control (Williams et al., 2007). Some of these may also be influenced by cortisol levels. Concerning the lack of cortisol effect on memory performance in MDD, a floor effect cannot be excluded, but seems unlikely as patients on average reached almost half of the maximum AMT score of 6 (see Table 1). Finally, the sample size was small, even though this is not uncommon in clinical challenge studies.

In summary, the present study replicates an impairing effect of hydrocortisone on autobiographical memory

retrieval in healthy participants (Buss et al., 2004). In addition, the results suggest a reduced GC sensitivity in patients with MDD as one possible explanation for the missing effect of hydrocortisone on AMT performance. Given the limitations of our study discussed above the current results are in need of a replication and extension using a multi-dimensional and multi-methodological assessment of glucocorticoid sensitivity.

Role of funding sources

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

Conflict of interest

None declared.

Acknowledgements

We would like to thank Dr. Hedda Ribbert for supporting recruitment of patients. Further, we would like to thank Miriam Antoine-Redeker who assisted with the proof-reading of the manuscript.

Appendix A

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

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

Appendix B

Classification of memories (mean, SD).

	Placebo		Hydrocortisone	
	MDD	Controls	MDD	Controls
Specific	2.81 (1.68)	4.44 (1.63)	2.94 (1.39)	3.25 (1.69)
Categoric	0.69 (1.08)	0.50 (0.82)	0.88 (0.81)	0.88 (1.41)
Extended	1.44 (1.59)	0.38 (0.62)	1.13 (1.02)	1.06 (1.12)
Non-memory	0.69 (0.70)	0.56 (0.89)	0.88 (0.89)	0.75 (0.68)

Specific: three elements are reported (location, time, persons, activities); Categoric: less than three elements are reported; Extended: event lasted longer than 1 day; Non-memory: no memory has been reported.

References

- Barden, N., 2004. Implication of the hypothalamic-pituitary-adrenal axis in the physiopathology of depression. *J. Psychiatry Neurosci.* 29 (3), 185–193.
- Barnhofer, T., Kuehn, E.M., de Jong-Meyer, R., 2005. Specificity of autobiographical memories and basal cortisol levels in patients with major depression. *Psychoneuroendocrinology* 30 (4), 403–411.
- Beck, A.T., Steer, R.A., 1994. Beck-Depressions-Inventar: BDI. Testhandbuch. Huber, Bern.
- Bremner, J.D., Vythilingam, M., Vermetten, E., Anderson, G., Newcomer, J.W., Charney, D.S., 2004. Effects of glucocorticoids on declarative memory function in major depression. *Biol. Psychiatry* 55 (8), 811–815.
- Buss, C., Wolf, O.T., Witt, J., Hellhammer, D.H., 2004. Autobiographic memory impairment following acute cortisol administration. *Psychoneuroendocrinology* 29 (8), 1093–1096.
- Campbell, S., Marriott, M., Nahmias, C., MacQueen, G.M., 2004. Lower hippocampal volume in patients suffering from depression: a meta-analysis. *Am. J. Psychiatry* 161 (4), 598–607.
- Coluccia, D., Wolf, O.T., Kollias, S., Roozendaal, B., Forster, A., de Quervain, D.J., 2008. Glucocorticoid therapy-induced memory deficits: acute versus chronic effects. *J. Neurosci.* 28 (13), 3474–3478.
- Dalgleish, T., Williams, J.M., Golden, A.M., Perkins, N., Barrett, L.F., Barnard, P.J., et al., 2007. Reduced specificity of autobiographical memory and depression: the role of executive control. *J. Exp. Psychol. Gen.* 136 (1), 23–42.
- De Kloet, E.R., Vreugdenhil, E., Oitzl, M.S., Joels, M., 1998. Brain corticosteroid receptor balance in health and disease. *Endocr. Rev.* 19 (3), 269–301.
- Egeland, J., Lund, A., Landro, N.I., Rund, B.R., Sundet, K., Asbjornsen, A., et al., 2005. Cortisol level predicts executive and memory function in depression, symptom level predicts psychomotor speed. *Acta Psychiatr. Scand.* 112 (6), 434–441.
- Gomez, R.G., Fleming, S.H., Keller, J., Flores, B., Kenna, H., DeBattista, C., et al., 2006. The neuropsychological profile of psychotic major depression and its relation to cortisol. *Biol. Psychiatry* 60 (5), 472–478.
- Holsboer, F., 2000. The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology* 23 (5), 477–501.
- Lupien, S.J., 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.
- Nemeroff, C.B., 1996. The corticotropin-releasing factor (CRF) hypothesis of depression: new findings and new directions. *Mol. Psychiatry* 1 (4), 336–342.
- Pariante, C.M., Thomas, S.A., Lovestone, S., Makoff, A., Kerwin, R.W., 2004. Do antidepressants regulate how cortisol affects the brain? *Psychoneuroendocrinology* 29 (4), 423–447.
- Parker, K.J., Schatzberg, A.F., Lyons, D.M., 2003. Neuroendocrine aspects of hypercortisolism in major depression. *Horm. Behav.* 43 (1), 60–66.
- Porter, R.J., Gallagher, P., Watson, S., Young, A.H., 2004. Corticosteroid–serotonin interactions in depression: a review of the human evidence. *Psychopharmacology* 173, 1–17.
- Van Vreeswijk, M.F., De Wilde, E.J., 2004. Autobiographical memory specificity, psychopathology, depressed mood and the use of the Autobiographical Memory Test: a meta-analysis. *Behav. Res. Ther.* 42 (6), 731–743.
- Webster, M.J., Knable, M.B., O'Grady, J., Orthmann, J., Weickert, C.S., 2002. Regional specificity of brain glucocorticoid receptor mRNA alterations in subjects with schizophrenia and mood disorders. *Mol. Psychiatry* 7 (9), 985–994.
- Williams, J.M., Barnhofer, T., Crane, C., Herman, D., Raes, F., Watkins, E., et al., 2007. Autobiographical memory specificity and emotional disorder. *Psychol. Bull.* 133 (1), 122–148.
- Williams, J.M., Broadbent, K., 1986. Autobiographical memory in suicide attempters. *J. Abnorm. Psychol.* 95 (2), 144–149.
- Wittchen, H.U., Zaudig, M., Fydrich, T., 1997. Strukturiertes Klinisches Interview für DSM-IV. Achse I: Psychische Störungen. SKID-I. Hogrefe.
- Wolf, O.T., 2008. The influence of stress hormones on emotional memory: relevance for psychopathology. *Acta Psychol. (Amst.)* 127 (3), 513–531.