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Effects of cortisol on the memory bias for emotional words? A study in patients with depression and healthy participants using the Directed Forgetting task

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ABSTRACT

Mood congruent alterations in information processing such as an impaired memory bias for emotional information and impaired inhibitory functions are prominent features of a major depressive disorder (MDD). Furthermore, in MDD patients hypothalamic–pituitary–adrenal axis dysfunctions are frequently found. Impairing effects of stress or cortisol administration on memory retrieval as well as impairing stress effects on cognitive inhibition are well documented in healthy participants. In MDD patients, no effect of acute cortisol administration on memory retrieval was found.

The current study investigated the effect of acute cortisol administration on memory bias in MDD patients (N = 55) and healthy controls (N = 63) using the Directed Forgetting (DF) task with positive, negative and neutral words in a placebo controlled, double blind design. After oral administration of 10 mg hydrocortisone/placebo, the item method of the DF task was conducted. Memory performance was tested with a free recall test.

Cortisol was not found to have an effect on the results of the DF task. Interestingly, there was significant impact of valence: both groups showed the highest DF score for positive words and remembered significantly more positive words that were supposed to be remembered and significantly more negative words that were supposed to be forgotten. In general, healthy participants remembered more words than the healthy controls. Still, the depressed patients were able to inhibit intentionally irrelevant information at a comparable level as the healthy controls. These results demonstrate the importance to distinguish in experimental designs between different cognitive domains such as inhibition and memory in our study.

1. Introduction

Mood congruent alterations in information processing such as an impaired memory bias for emotional information and deficits in inhibitory functions such as suppression of irrelevant information are prominent features of a major depressive disorder (MDD). Furthermore, an MDD is characterized by alterations of the hypothalamus pituitary adrenal (HPA) axis, e.g., higher cortisol release and impaired feedback sensitivity probably due to reduced glucocorticoid receptor functions (Calfa et al., 2003; Holsboer, 2000; Pariante and Lightman, 2008; Parker et al., 2003; Webster et al., 2002). Interestingly, there is some evidence that higher cortisol levels are associated with impairments of memory and of executive function in MDD patients (Abercrombie et al., 2011; Gomez et al., 2009; Hinkelmann et al., 2009; Schlosser et al., 2011). In healthy participants, the effects of acute stress and of acute cortisol administration on memory functions are well documented with impairing effects on memory retrieval (Gagnon and Wagner, 2016; Het et al., 2005; Wingenfeld and Wolf, 2014). The impairing effect can be modulated e.g. by the emotionality of the memory content (Kuhlmann et al., 2005), the test situation (Kuhlmann and Wolf, 2006) or the use of oral contraceptives in women (Kuhlmann and Wolf, 2005) and has not been found in

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older people (Hidalgo et al., 2015; Pulopulos et al., 2013). In MDD patients, most studies found no effect of acute cortisol administration on memory retrieval (Schlosser et al., 2010; Terfehr et al., 2011a, b; Wingenfeld and Wolf, 2015) which has been interpreted in line with the hypothesis of a reduced glucocorticoid receptor function (Holsboer, 2000; Webster et al., 2002). As well, one study investigating inhibitory response performance in MDD patients, found no effects of an acute cortisol administration (Schlosser et al., 2013). Overall, in healthy participants stress rather than cortisol administration seems to impair cognitive inhibition, while response inhibition is even enhanced by stress (Shields et al., 2016).

Inhibition is an important mechanism to regulate emotions and unwanted cognitions, and inhibitory deficits have been associated with rumination, poor treatment response and relapse in MDD patients (Joormann, 2010). Therefore, it seems to be of great importance to get a better understanding of the underlying mechanisms of inhibition deficits in MDD patients. Established neuropsychological paradigms to measure response inhibition are the Stroop task (Stroop, 1992) and the Go/No-Go task (Menon et al., 2001). Studies using these tasks could demonstrate deficits in response inhibition in MDD patients (Gotlib and Joormann, 2010; Peckham et al., 2010; Wingenfeld and Wolf, 2015). Another paradigm to investigate inhibition ability is the Directed Forgetting (DF) task. Instead of response times it measures memory and the intentional suppression of irrelevant information (Domes et al., 2006) and therefore goes beyond the Stroop or Go/NoGo tasks. As it measures the intentional inhibition of memory, the DF task might indicate a more conscious part of inhibition. Deficits in the inhibition of unwanted thoughts and memories are common in MDD patients and may lead to increased negative thoughts and a negativity bias in memory. Indeed, MDD patients were found to have deficits in the ability to forget negative stimuli compared to positive or neutral stimuli (Power et al., 2000; Yang et al., 2016b). A study in MDD patients using the DF task with neutral words showed that depressed patients recalled more words of the to be forgotten condition and less words of the to be remembered condition compared to healthy controls (Cottencin et al., 2008). Another study using the DF task with anxiety- and depression-related words showed that MDD patients as well as patients with anxiety and somatization disorders had difficulties to remember these words compared to neutral words in the to be remembered condition and difficulties to forget these words compared to neutral words in the to be forgotten condition (Wingenfeld et al., 2013). These studies indicate difficulties in the intentional suppression of irrelevant information, especially when negative or illness-related, in MDD patients.

The current study aimed to investigate the effect of an acute cortisol administration on memory bias in MDD and healthy controls using the item method of the DF task, in which participants are instructed to either remember or to forget the item that is presented next, with emotionally valenced (positive and negative) and neutral words. According to previous results (Power et al., 2000; Yang et al., 2016b), we hypothesized a memory bias for negative words in the group of MDD patients, meaning more remembered negative words compared to positive and neutral words independent of the to be remembered or to be forgotten condition. For cortisol administration, we hypothesized an interaction by group with impairing effect of cortisol on the DF effect in the healthy control group according to the reported impairing cortisol effects on memory retrieval in the literature (de Quervain et al., 2000; Gagnon and Wagner, 2016; Het et al., 2005; Wingenfeld and Wolf, 2014), and no effect of cortisol in the group of depressed patients as most studies in MDD patients found no effect of acute cortisol administration on memory retrieval or inhibitory response performance (Schlosser et al., 2010, 2013; Terfehr et al., 2011a, b; Wingenfeld and Wolf, 2015).

2. Material and methods

2.1. Participants

Fifty-five depressed inpatients (31 women, 24 men; mean age: 34.2 years, SD: 9.2 years) and 63 healthy control participants (40 women, 23 men; mean age: 31.7 years, SD: 10.3 years) were included. All patients and healthy control participants were reported on in previous studies from our group (MDD $N = 16$, controls $N = 16$ (Schlosser et al., 2010); MDD $N = 44$, controls $N = 51$ (Terfehr et al., 2011a); MDD $N = 57$, controls $N = 56$ (Terfehr et al., 2011b); MDD $N = 54$, controls $N = 54$ (Schlosser et al., 2013)). Patients were recruited at the Department of Psychiatry and Psychotherapy Bethel, Ev. Hospital Bielefeld, Germany, and at the Department of Psychosomatic Medicine and Psychotherapy, University Medical Center Hamburg-Eppendorf and Schoen Klinik Hamburg-Eilbek, Germany.

Inclusion criterion for the patient group was a current diagnosis of a depressive episode. Exclusion criteria were dementia, cognitive impairment, current or lifetime schizophrenia, schizoaffective disorder, major depression with psychotic symptoms, bipolar disorder, current anorexia, substance dependence, attention-deficit/hyperactivity disorder, CNS relevant somatic diseases, neurological diseases, metabolic diseases, organic shift in cortisol secretion, immune-mediated diseases, severe cardiovascular diseases, current infections, use of beta-blockers or benzodiazepines, pregnancy or nursing. Psychiatric diagnoses were established by trained psychologists using the Structured Clinical Interview for DSM-IV (SCID-I (Wittchen et al., 1997)). Severity of depressive symptoms was assessed by means of the Beck Depression Inventory (BDI (Beck et al., 1994)).

Healthy control participants recruited by local advertising. All control participants were free of former and present DSM-IV Axis I disorders according to the SCID-I and had no physical illness. Healthy controls received financial remuneration for their efforts (100 €).

Written informed consent was obtained from all participants after the nature of the procedures had been fully explained. The study was carried out in accordance with the latest version of the Declaration of Helsinki and approved by the University of Muenster Ethics Committee and the Ethics Committee of the Medical Council of Hamburg.

All MDD patients and healthy control participants were tested in a double-blind placebo-controlled design with quasi-randomized test order and received either a dosage of 10 mg of hydrocortisone (Jenapharm®) or a placebo. Of the patient group, 26 patients received hydrocortisone and 29 received a placebo. Of the healthy control group, 31 participants received cortisol and 32 received a placebo.

2.2. Material

The Directed Forgetting (DF) task is a widely studied experimental memory control paradigm (Zwissler et al., 2011) which measures intentional suppression of irrelevant information (Domes et al., 2006). Memory control is important to select between relevant and non-relevant memory content that is needed e.g. for a successful and focused task performance without memory distraction (Bjork et al., 1998). In the DF task, one portion of the presented material is designated as “to be remembered”, the other portion as “to be forgotten” after presentation. In general, previous results show that the instruction “to be remembered” or “to be forgotten” leads to a better recall of the “to be remembered”

material vs. the "to be forgotten" material. In the following, we will refer to the difference of the "to be remembered" and the "to be forgotten" material as the "DF score". MacLeod (1999) could show that this effect is independent of social desirability or motivational demands. In this study, we used the item method of the DF task, in which participants are instructed to either forget or remember each item immediately after it has been presented. Overall, 42 words were presented – 14 for each of the valence categories: positive, negative and neutral. Seven words of each category were to be remembered and 7 were to be forgotten. Word stimuli were selected on the basis of norms in the German language, i.e. emotionality, familiarity, statistical frequency in the German language (Borsutzky et al., unpublished). Word stimuli were presented on a 17-inch monitor of a standard PC using the software presentation 7.76. Each word was presented for 2000 ms, followed by an instruction to remember or to forget the word that was presented for 3000 ms. Immediately afterwards, memory testing was conducted. In a free recall test, the participants were asked to name all words that they could remember. All words - to be remembered, to be forgotten or new words (intrusions) - were registered.

2.3. Procedures

Testing was conducted by trained psychologists. Participants were tested individually in a quiet room and seated approx. 50 cm in front of a computer screen. Each participant was tested in a double-blind placebo-controlled design with quasi-randomized test order and received either a dosage of 10 mg of hydrocortisone or a placebo. Drugs were administered orally 45 min prior to testing, which took place between 1600 h and 1800 h. Saliva was collected 10 min before (baseline), 45 min (sample +45) and 90 min (sample +90) after cortisol administration, using saliva collection devices (Sarstedt AG, Nuembrecht, Germany). After being stored at room temperature until the session was completed the saliva was kept at −80 °C until the biochemical analyses. Salivary cortisol levels were determined using a commercial radioimmunoassay (IBL, Hamburg, Germany). Interassay and intraassay coefficients of variation were below 8%. All biochemical analyses were carried out by the Department of Biological Psychiatry, University Medical Center Hamburg-Eppendorf. For some samples the amount of saliva collected was insufficient for the analyses. Therefore, cortisol levels were only obtained from 42 patients and 39 control participants.

2.4. Statistical analyses

Differences in demographic characteristics between the patient group (N = 55) and the healthy participants (N = 63) were compared using one-way analyses of variance (ANOVAs) for continuous variables and χ^2-tests for dichotomous variables.

In the analyses that are described below, the belonging to the patient group or to the control group served as an quasi-experimental factor ("group") and the quasi-randomized assignment to the treatment (placebo vs. cortisol) served as an experimental factor ("treatment"). Twenty-nine patients and 32 controls received a placebo, while 26 patients and 31 controls received cortisol.

We calculated the DF score as the difference of the number of remembered words that were supposed to be remembered vs. the number of remembered words that were supposed of to be forgotten. To analyse the influence of cortisol and depression on the DF score, we used a 2 x 2 ANOVA with the factors "group" (patients vs. healthy participants) and "treatment" (placebo vs. cortisol) and the DF score as dependent variable.

As a proof of concept, we additionally analysed the DF score itself. Therefore, we used the raw data of the number of remembered words that were supposed to be remembered vs. the number of remembered words that were supposed of to be forgotten and analysed if there was a significant difference. Therefore, we used a 2 x 2 x 2 ANOVAs for repeated measures with one within-subject factor "DF score" (number of remembered words that were supposed to be remembered vs. number remembered words that were supposed of to be forgotten) and two between-subject factors, "group" (patients vs. healthy participants) and "treatment" (placebo vs. cortisol). The DF score served as dependent variable.

In the next step, we took the impact of valence into account. To analyse DF scores according to each valence category, we used a 2 x 3 x 2 x 2 ANOVA for repeated measures with two within-subject factors, "DF score" (number of remembered words that were supposed to be remembered vs. number remembered words that were supposed of to be forgotten), and "valence" (neutral vs. negative vs. positive), and two between-subject factors, "group" (patients vs. healthy participants) and "treatment" (placebo vs. cortisol).

For a deeper understanding of the "valence" effect, we additionally analysed the "valence" effect separately for words that should be remembered and words that should be forgotten. We used two 3 x 2 x 2 ANOVAs for repeated measures with one within-subject factor "valence" (number of remembered words of the to be remembered/to be forgotten words of neutral vs. negative vs. positive words) and two between-subject factors, "group" (patients vs. healthy participants) and "treatment" (placebo vs. cortisol).

As a manipulation check, levels of saliva cortisol were analysed using a 3 x 2 x 2 ANOVA for repeated measures with the within-subject factor "time" (measurement time 1 vs. measurement time 2 vs. measurement time 3) and the between-subject factors "treatment" (placebo vs. cortisol) and "group" (patients vs. healthy participants). We could conduct this analysis only for a reduced sample, since cortisol levels could only be obtained from 42 patients (24 with placebo, 18 with cortisol) and 39 control participants (19 with placebo, 20 with cortisol).

Bonferroni corrected post-hoc t-tests were used to further compare differences between the three emotional valences and between treatment conditions if appropriate.

To control for potentially confounding variables, demographic variables showing differences between groups were included as covariates using one-way analyses of covariance (ANCOVAs) for repeated measures. To control for the use of psychotropic medication and potential effects of sex, we included "use of psychotropic medication" and "sex" as additional covariates as well.

A p-value smaller than 0.05 was considered to indicate statistical significance.

3. Results

3.1. Demographic variables

MDD patients and healthy controls did not differ significantly in age (T (df = 116) = 1.37, p = 0.17), sex (χ^2 = 0.43), education (schooling years; T (df = 116) = 1.6, p = 0.11) or current intake of oral contraceptives (χ^2 = 0.11), but in current smoking (χ^2 < 0.01). Therefore, "smoking" was included as covariate in further analyses.

For demographic characteristics please see Table 1.

As expected, patients were more depressed as control participants according to the BDI (*see* Table 1). 54.5% of patients were diagnosed with recurrent depressive disorder and they reported a median of one prior admission to inpatient treatment. Mean length of the current episode was 22 weeks.

In addition to the diagnosis of a current major depression, nine patients fulfilled the criteria for one or more psychiatric comorbidities (2 x general anxiety disorder, 4 x social phobia, 1 x panic

Table 1
Demographic characteristics.

	MDD patients (N = 55)	Healthy participants (N = 63)	p/χ^2
Mean age, years (SD)	34.2 (9.2)	31.7 (10.3)	n.s.
Women, %	56.4	63.5	n.s.
Education, years (SD)	11.3	11.7	n.s
Intake of oral contraceptives (currently), %	11.1	27.1	n.s.
Smokers (currently), %	63.6	34.9	$\chi^2 < 0.01$
BDI, mean (SD)	23.0 (9.0)	3.0 (3.5)	$p < 0.01$

SD= Standard deviation, N= Number, MDD = Major depressive disorder, BDI= Beck's Depression Inventory.

disorder, 2 x specific phobia, 1 x unspecific eating disorder, 1 x compulsive disorder, 1 x somatoform disorder).

Forty-six patients were treated with psychotropic medication: selective serotonin reuptake inhibitors (N = 19), serotonin–norepinephrine reuptake inhibitors (N = 11), selective serotonin norepinephrine reuptake inhibitors (N = 4), norepinephrine reuptake inhibitors (N = 2), norepinephrine-dopamine reuptake inhibitors (N = 1), tricyclic antidepressants (N = 4), monoamine oxidase inhibitors (N = 1), melatonergic antidepressants (N = 3), atypical antidepressants (N = 4), (atypical) antipsychotics (N = 9), nonbenzodiazepine hypnotics (N = 1), sedativas (N = 1). To control for the use of psychotropic medication, "use of psychotropic medication" was included as covariate in further analyses.

3.2. Cortisol levels

Cortisol measurements could be conducted for 42 patients (24 with placebo, 18 with cortisol) and 39 healthy controls (19 with placebo, 20 with cortisol). The ANOVA for repeated measures showed a significant effect of "time" ($F(df = 2,154) = 51.09$, $p < 0.01$), a significant effect of "treatment" ($F(df = 1,77) = 75.78$, $p < 0.01$) and a significant interaction of "time" x "treatment" ($F(df = 2,154) = 48.54$, $p < 0.01$). In the placebo condition, means of cortisol levels were 2.07 ng/ml (SD: 1.55) at measurement time 1, 2.75 ng/ml (SD: 6.13) at measurement time 2 and 2.41 ng/ml (SD: 6.38) at measurement time 3. In the cortisol condition, means of cortisol levels were 2.89 ng/ml (SD: 3.14) at measurement time 1, 47.49 ng/ml (SD: 33.80) at measurement time 2 and 26.12 ng/ml (SD: 23.42) at measurement time 3. The effect of "group" ($F(df = 1,77) = 1.52$, $p = 0.22$), the interaction of "time" x "group" ($F(df = 2,154) = 1.52$, $p = 0.22$) and the interaction of "time" x "treatment" x "group" ($F(df = 2,154) = 0.91$, $p = 0.40$) were not significant. Cortisol levels at measurement time 1 (baseline) did not differ between placebo and cortisol treatment ($T(df = 59) = 1.35$, $p > 0.10$), but at measurement time 2 ($T(df = 45) = 8.73$, $p < 0.01$) and measurement time 3 ($T(df = 50) = 6.70$, $p < 0.01$). There were no differences in cortisol levels between groups at measurement time 1, 2 or 3 (all $p > 0.10$).

Including "sex", "smoking" and "use of psychotropic medication" as covariates did not change the effects of these analyses.

3.3. Directed Forgetting task

3.3.1. Directed Forgetting score

Regarding the DF score, we found no significant effects of "group" ($F(df = 1,114) = 0.25$, $p = 0.62$), "treatment" ($F(df = 1,114) = 0.07$, $p = 0.79$) and of the interaction "group" x "treatment" ($F(df = 1,114)<0.01$, $p = 0.97$).

Additionally, we analyzed the raw data of the DF score to see if the DF task worked out as expected. Therefore, we analyzed the difference of the number of remembered words that were supposed to be remembered vs. the number of remembered words that were supposed to be forgotten, taking influences of "group" and "treatment" into account. The results showed a significant main effect for the to be remembered vs. the to be forgotten words ($F(df = 1,113) = 304.45$, $p < 0.01$). The effects "group" ($F(df = 1,113) = 2.66$, $p = 0.11$) and the effect "treatment" ($F(df = 1,113) = 0.30$, $p = 0.58$) were not significant. There was no significant interaction (all $p > 0.10$). As expected, significantly more words were remembered of the to be remembered words compared to the to be forgotten words. *Please see also* Table 2.

Including "sex", "smoking" and "use of psychotropic medication" as covariates did not change the effects.

3.3.2. Emotional valence

When analysing DF scores according to each valence category, we found significant main effects of "DF score" ($F(df = 1,113) = 341.55$, $p < 0.01$), of "valence" ($F(df = 2,226) = 97.08$, $p < 0.01$) and of "group" ($F(df = 1,113) = 4.00$, $p < 0.05$). The effect "treatment" ($F(df = 1,113) = 0.05$, $p = 0.83$) was not significant. Furthermore, we found a significant interaction of "DF score" x "valence" ($F(df = 2,226) = 31.37$, $p < 0.01$). There was no other significant interaction (all $p > 0.10$). As expected, significantly more words were remembered of the to be remembered words compared to the to be forgotten words. Post hoc tests revealed that the DF score was significantly higher for positive valence (Fig. 1). Overall, the healthy control participants remembered more words than the MDD patients. However, when "sex", "smoking" and "use of psychotropic medication" were included as covariates, the main effect "group" was significant only at trend level ($F(df = 1,110) = 3.01$, $p = 0.08$). All other effects did not change when these covariates were included.

Additionally, the number of recalled words which were supposed to be remembered and those which were supposed to be forgotten were analysed separately. We found a significant effect of "valence" for the words that were supposed to be remembered ($F(df = 2,226) = 70.27$, $p < 0.01$). The effects "group" ($F(df = 1,113) = 1.37$, $p = 0.24$) and "treatment" ($F(df = 1,113) = 0.01$, $p = 0.93$) and the interactions (all $p > 0.10$) were not significant. Post hoc analyses showed that significantly more positive words compared to neutral and negative words were remembered (Fig. 2a,c). Including "sex", "smoking" and "use of psychotropic medication" as covariates did not change the effects.

For the words that were supposed to be forgotten, we found a significant effect of "valence" ($F(df = 2,228) = 48.65$, $p < 0.01$) and of "group" ($F(df = 1,114) = 4.04$, $p < 0.05$). The effect "treatment" ($F(df = 1,114) = 0.04$, $p = 0.85$) was not significant. There was no significant interaction (all $p > 0.10$). Post-hoc tests revealed that significantly more negative words were remembered compared to neutral and positive words (Fig. 2b). Overall, healthy participants remembered more words compared to the depressed patients. The difference was significant for neutral and negative words (Fig. 2d). When "sex", "smoking" and "use of psychotropic medication" were included as covariates, the main effect "group" was only significant

Table 2
Number of words of the Directed Forgetting score, the to be remembered and the to be forgotten words.

		MDD[a] patients	Healthy participants
Directed Forgetting score	placebo	5.34 (2.68)	5.63 (3.89)
(mean number of words, SD[a])	cortisol	5.15 (3.81)	5.48 (2.76)
	total	5.25 (3.23)	5.56 (3.35)
Words supposed to be remembered	placebo	7.17 (2.75)	7.94 (3.21)
(mean number of remembered words, SD[a])	cortisol	7.35 (3.44)	7.90 (2.25)
	total	7.25 (3.07)	7.92 (2.77)
Words supposed to be forgotten	placebo	1.83 (1.34)	2.31 (1.53)
(mean number of remembered words, SD[a])	cortisol	2.19 (2.33)	2.53 (1.85)
	total	2.00 (1.87)	2.42 (1.68)

[a] SD= Standard deviation, MDD = Major depressive disorder.

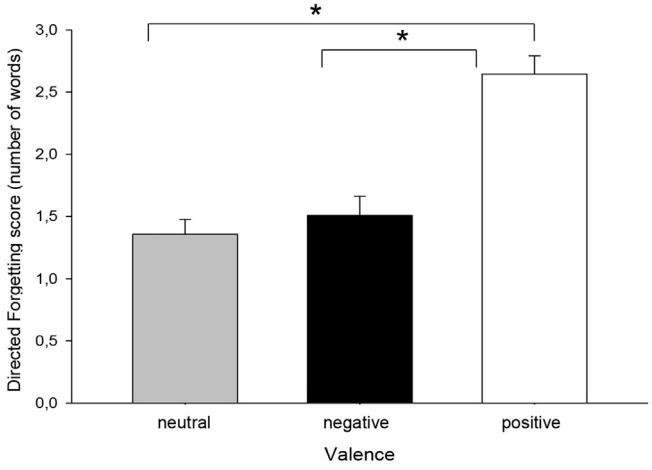

Fig. 1. Directed forgetting score (mean number of remembered words that were supposed to be remembered vs. mean number of remembered words that were supposed to be forgotten) according to valence (accumulated for both groups and both treatments). * indicates $p < 0.05$.

at trend level ($F(df = 1,109) = 3.66$, $p = 0.06$). All other effects did not change when these covariates were included.

4. Discussion

In the current study, we aimed to investigate the effect of an acute cortisol administration on memory inhibition in MDD patients and healthy controls using the item method of the Directed Forgetting (DF) task. Here, the participants were instructed to either remember or to forget the item that is presented next, using emotionally valenced, i.e. positive and negative, and neutral words. As expected, both groups remembered more to be remembered than to be forgotten words resulting in a significant DF effect. In contrast to our prediction, we did not find a significant impact of cortisol on performance in the DF task, neither in the healthy participants nor in the MDD patients. However, we found a significant impact of valence with the highest DF score for positive words in both groups.

That we did not find a significant impact of cortisol is in line with results of a recent meta-analysis (Shields et al., 2016) showing that stress, but not cortisol administration had impairing effects on cognitive inhibition. Interestingly, results of that meta-analysis for response inhibition differed significantly from results for cognitive inhibition. On response inhibition, stress had overall enhancing effects and cortisol administration time dependent effects. While there is evidence that cognitive and response inhibition share in general the same underlying processes, at least in healthy participants (Friedman and Miyake, 2004), another study in children with attention-deficit hyperactivity disorder demonstrated that these processes can dissociate under certain circumstances (Johnstone et al., 2009). For the specific stress effects on cognitive inhibition, it has been suggested that other factors than just the concentration of cortisol related to stress might be important such as further components of the HPA axis (e.g. corticotropin-releasing hormone, adrenocorticotropic hormone) or other hormone systems (e.g. sex hormone systems), immune system factors, or catecholaminergic activity (Shields et al., 2016). However, a study in healthy participants showed that a psychosocial stressor did not affect the performance in a DF task (Zwissler et al., 2011), while other studies investigating the related phenomenon of retrieval induced forgetting found that stress, but not cortisol administration, vanished inhibition effects (Koessler et al., 2009, 2013). This suggests that underlying processes of intentional memory inhibition as required for the DF task might somehow differ from cognitive inhibition in other tasks. For memory on the other hand, effects of stress and cortisol are well documented for healthy participants (Gagnon and Wagner, 2016; Het et al., 2005; Schwabe, 2013; Wingenfeld and Wolf, 2014). For MDD patients, impaired memory performance and response inhibition compared to healthy controls have been reported, but without further impact of cortisol administration (Wingenfeld and Wolf, 2015). It has been speculated that the missing cortisol effect - in contrast to healthy individuals - might reflect reduced central glucocorticoid sensitivity. Regarding this point, we cannot draw any conclusions from our results, though. However, we could replicate the effect of an impaired memory performance in MDD patients compared to healthy controls. Overall, healthy participants remembered more words as the MDD patients, statistically significant for the words that were supposed to be forgotten.

Regarding the size of DF score, we did not find significant differences between the MDD patients and the healthy participants. This result suggests that the depressed patients were able to inhibit intentionally irrelevant information at a comparable level as the healthy controls. This is in contrast to other studies which showed deficits of MDD patients in the ability to inhibit memory content, especially for negative and anxiety- and depression-related stimuli (Cottencin et al., 2008; Power et al., 2000; Wingenfeld et al., 2013; Yang et al., 2016b). A potential explanation for this discrepancy might be the selection of our word stimuli. A recent event related potential study (Gallant and Dyson, 2016) could demonstrate that valence and arousal of stimuli have both a distinct impact on the performance in the DF task. Our selection of negative words was rather general with little relation to depression or the personal situation of the patients or participants. Thus, the arousal caused by the negative words might have been comparatively low. The inhibition deficits in MDD patients might be better visible when material is used that is related to the present disorder or in a different way personally relevant. Unfortunately, we have no ratings of the subjective arousal or valence for the word material from the

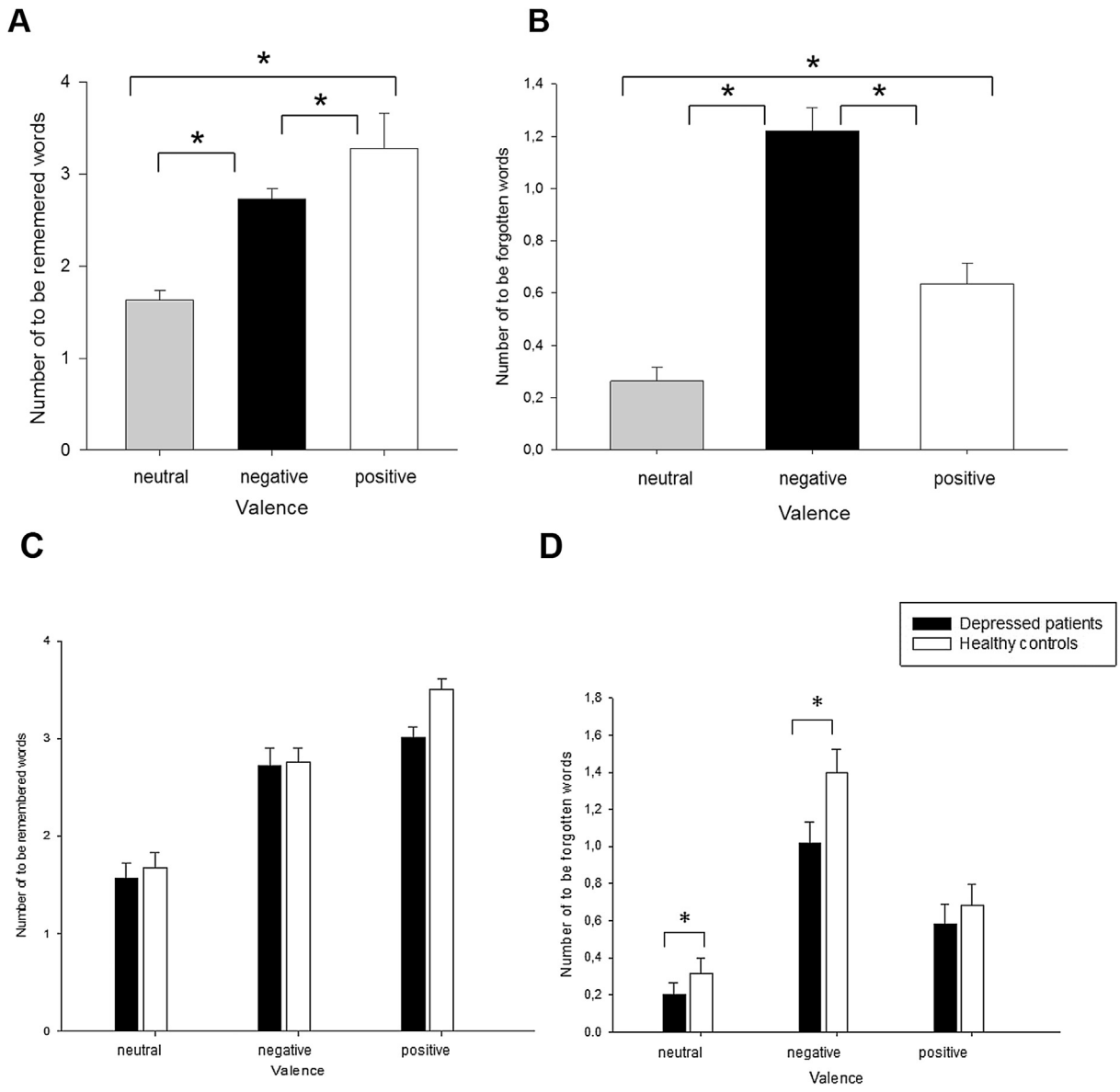

Fig. 2. Mean number of remembered words according to valence (accumulated for both groups and both treatments) of the words that were supposed to be remembered (Fig. A) and of the words that were supposed to be forgotten (Fig. B). Mean number of remembered words according to valence (separately for depressed patients and healthy controls) of the words that were supposed to be remembered (Fig. C) and of the words that were supposed to be forgotten (Fig. D). * indicates $p < 0.05$.

patients or healthy participants.

As a further important result, we found a significant impact of valence: both groups showed the highest DF score for positive words. This result suggests that a positive valence of the words seemed to facilitate the DF task. Further analyses of the memory performance showed that both groups remembered significantly more positive words of the words that were supposed to be remembered. Of the words that were supposed to be forgotten, both groups remembered significantly more negative words. This suggests that negative words were most difficult to suppress.

Emotional material is in general more likely to be remembered than neutral material (e.g (Buchanan et al., 2006; Cahill and McGaugh, 1995; Hamann, 2001).,). Moreover, it has been found that negative stimuli are more difficult to forget intentionally for healthy and depressed patients (e.g (Chen et al., 2012; Cottencin et al., 2008; Minnema and Knowlton, 2008; Power et al., 2000; Wingenfeld et al., 2013).,). Behavioural outcomes are supported by several studies investigating the underlying central processes using EEG and fMRI methods (e.g., (Brandt et al., 2013; Hauswald et al., 2011; Yang et al., 2016a,b; Yang et al., 2012)).

However, only few studies used positive valenced stimulus material in the DF task with rather heterogeneous results. Findings in healthy participants and patients with anxiety disorders vary from no impact of valence (Gallant and Yang, 2014; Tolin et al., 2002) to more false alarms for memory of positive pictures (Zwissler et al., 2011) to attenuated DF scores for positive material (Moulds and Bryant, 2002; Wilhelm et al., 1996) and to greater DF scores for socially positive words (Liang et al., 2011).

Some limitations of our study should be mentioned. First, we did not assess subjective valence and arousal ratings for the word material from the patients or healthy participants. Therefore, we cannot determine specific effects of arousal and valence for the results. Additionally, most patients were medicated, which could have had an influence on the HPA axis functioning, glucocorticoid

receptor sensitivity as well as memory performance (Pariante et al., 2004), although including the use of psychotropic medication as a covariate did not change the results. Therefore, it would be interesting to investigate cortisol effects on DF in a sample of medication-free MDD patients in future studies. Furthermore, we did not assess if control participants had a first degree relative with a psychiatric disorder. Memory deficits have also been found in first degree relatives (Quraishi et al., 2009). As a further limitation, we did not control for potential effects of phases of the menstrual cycle in female participants, even though it has been demonstrated that the menstrual cycle phase has impact on the activity of the HPA axis (Kirschbaum et al., 1999).

In sum, our results concerning the emotional valence of the word stimuli demonstrate that a positive valence of the words seemed to facilitate the performance in the DF task while negative words seemed to be most difficult to suppress. Interestingly, this was the case for healthy participants as well as for MDD patients.

That negative words seemed to be most difficult to suppress might have important clinical implications. Since MDD patients in our sample were able to inhibit memory content at a comparable level as the healthy participants, we can rather not assume from our data that a memory inhibition deficit might work as a specific mechanism for the development of a depressive disorder. However, a general difficulty to suppress negative memory content could play a role as a perpetuating factor in major depression.

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Appendix 1

Words used in the Directed Forgetting task *(translated from German)*.

Word list I*			Word list II*		
neutral	negative	positive	neutral	negative	positive
minute	misery	joy	section	funeral	holidays
number	suffering	hope	tag	massacre	leisure
program	torture	love	button	enemy	humor
sort	shame	paradise	switch	violence	music
table	bale	summer	schema	killer	beauty
process	doom	trust	procedure	murder	confidence
citation	coercion	coziness	template	forest fire	forest

*Word list I and II served in a quasi-randomized order as wort material for the to be remembered and to be forgotten items, respectively.

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