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Effects of acute cortisol administration on response inhibition in patients with major depression and healthy controls

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ABSTRACT

Glucocorticoids (GCs) have repeatedly been shown to impair hippocampus-mediated, declarative memory retrieval and prefrontal cortex-based working memory in healthy subjects. However, recent experimental studies indicated that patients with major depressive disorder (MDD) lack these impairing effects. These missing effects have been suggested to result from dysfunctional brain GC receptors. The purpose of the present study was to investigate whether response inhibition, an executive function relying on the integrity of the prefrontal cortex, would be impaired after cortisol administration in patients with MDD. In a placebo-controlled, double blind crossover study, 50 inpatients with MDD and 54 healthy control participants conducted an emotional go/no-go task consisting of human face stimuli (fearful, happy, and neutral) after receiving a dose of 10 mg hydrocortisone and after placebo. GC administration had an enhancing effect on inhibitory performance in healthy control participants, indicated by faster responses, while no GC effect was revealed for the patients group. Moreover, patients showed an overall worse performance than healthy participants. In conclusion, this study further supports the hypothesis of impaired central glucocorticoid receptor function in MDD patients. Regarding the importance of inhibitory functioning for daily living, further studies are needed to examine the impact of glucocorticoids on response inhibition.

1. Introduction

In the last decades, neuroendocrine research has indicated that glucocorticoids (GCs) affect cognitive performance, particularly hippocampus-mediated declarative memory and prefrontal cortex-mediated working memory for emotional material (Belanoff et al., 2001; Het et al., 2005; de Quervain et al., 2008; Wolf, 2009). This evidence is of high relevance for major depressive disorder (MDD) which has been characterized by both cognitive dysfunctions and glucocorticoid alterations.

About 50–70% of patients with MDD are characterized by functional abnormalities of the hypothalamus–pituitary–adrenal (HPA) axis including cortisol hypersecretion (Parker et al., 2003; Barden, 2004; Pariante and Lightman, 2008) and a reduced peripheral sensitivity of glucocorticoid receptors (GR) (Holsboer, 2000; Calfa et al., 2003). GRs are widely distributed throughout the brain and are found in high densities in the hippocampus and the prefrontal cortex (PFC; Patel et al., 2000; de Kloet, 2003), two brain areas closely related to cognitive function.

One of the major cognitive impairments in MDD is PFC mediated executive dysfunction (Ottowitz et al., 2002; Rogers et al., 2004; Beblo et al., 2011). A key component of executive functions is referred to as 'inhibitory control' which allows inhibiting the processing of irrelevant information and thereby impacts working memory efficiency (Hasher et al., 1999). Understanding the underlying mechanisms of inhibition deficits in MDD

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is of special interest, as inhibitory deficits have been associated with rumination, poor treatment response and relapse (Joormann, 2010). Inhibition is usually examined by paradigms assessing response inhibition which refers to the ability to withhold a pre-potent cognitive or motor response (Lezak, 1995). Prominent tasks to investigate response inhibition are the Stroop Color and Word Test (SCWT, Stroop, 1935) and Go/No-Go tasks (e.g. Menon et al., 2001). Using these tasks with either neutral or emotional stimuli, several studies yielded impairments in response inhibition in patients with MDD indicated by slower response times and/or more errors of commission compared to healthy control subjects (Degl'Innocenti et al., 1998; Murphy et al., 1999; Schatzberg et al., 2000; Kaiser et al., 2003; Stordal et al., 2004; Langenecker et al., 2005; Markela-Lerenc et al., 2006; Gohier et al., 2009), even in a remitted state (Biringer et al., 2005; Paelecke-Habermann et al., 2005; Nakano et al., 2008). These impairments have been related to structural and functional brain abnormalities, particularly volume reduction and hypoactivation of the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) (Davidson et al., 2002; Ottowitz et al., 2002; Rogers et al., 2004).

Neuroendocrine research has provided accumulating evidence for an interrelationship between HPA axis dysregulation and deficits mainly in declarative memory, working memory and executive functions in patients with MDD, although the results are inconclusive and almost exclusively based on correlational data (for a recent review see Schlosser et al., 2011). Regarding response inhibition, cross-sectional studies indicated significant associations between measures of HPA axis function and inhibitory deficits on the SCWT in MDD patients (Egeland et al., 2005; Gomez et al., 2006), though not all studies agree (Gomez et al., 2009). To date, there is a paucity of studies investigating the acute effect of GCs on cognitive function in MDD. Bremner et al. (2004) were the first to investigate the impact of GCs on declarative memory in depressed patients and they found memory performance to be improved after chronic dexamethasone treatment in MDD patients, while being unchanged in healthy controls. In three recent experimental studies from our group, we consistently found that after a single administration of 10 mg hydrocortisone declarative and working memory were impaired in healthy participants, while memory performance in MDD patients was unaffected (Schlosser et al., 2010; Terfehr et al., 2011a, 2011b). Altogether, these results have been interpreted as first experimental evidence for a reduced central (brain) GR sensitivity in patients with MDD (Rohleder et al., 2010; Schlosser et al., 2011). To our knowledge, only four studies investigated the effect of acute cortisol elevation on inhibitiory control in healthy subjects (Wolf et al., 2001; Oei et al., 2009; Scholz et al., 2009; Zwissler et al., 2011). Scholz et al. (2009) demonstrated that a single psychosocial stress induction (Trier Social Stress Test, TSST) significantly impaired go/no-go performance in healthy men. In contrast, Zwissler et al. (2011) found inhibitory control of memory in a directed forgetting task not to be affected after a psychosocial stress induction (TSST) in healthy participants. Accordingly, Wolf et al. (2001) found no impairing effect of acute cortisol administration on SCWT performance in healthy men. Oei et al. (2009) even found an enhancing effect of hydrocortisone on inhibitory performance when examining distracter interference in a Sternberg working memory task in healthy men.

Effects of acute GC administration on executive functions in MDD other than working memory have not yet been studied. Thus, the purpose of the present study was to examine the effects of an acute GC administration on prefrontal cortex dependent executive functions, particularly response inhibition, in patients with MDD. First, due to a reduced central GR sensitivity, we proposed that hydrocortisone administration would not affect inhibitory performance in patients with MDD. Considering previous research on GC effects on declarative and working memory, we secondly predicted that inhibitory performance of healthy control participants would be impaired after hydrocortisone treatment compared to placebo treatment particularly when inhibiting emotional stimuli. Third, we hypothesized patients with MDD to perform generally worse in inhibitory control compared to non-depressed control participants.

In order to test these hypotheses, we utilized a placebo-controlled, double-blind, crossover design. After hydrocortisone and placebo treatment, respectively, 50 inpatients with MDD and 54 healthy control participants, matched for age, sex and years of education, conducted an emotional visual go/no-go task known to measure the ability to inhibit a pre-potent motor response.

2. Methods

2.1. Participants

Fifty-two inpatients (31 females, 21 males) and fifty-four healthy control participants (35 females, 19 males) were initially enrolled in this study. All patients and healthy control participants were reported on in previous studies from our group (Schlosser et al., 2010, MDD $n=16$, controls $n=16$; Terfehr et al., 2011a, MDD $n=44$, controls $n=51$; Terfehr et al., 2011b, MDD $n=57$, controls $n=56$). 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 criteria for patients were a current MDD, single or recurrent according to DSM-IV criteria, and for both patients and control participants an age from 18 to 60 years. Criteria for exclusion for patients were current or lifetime schizophrenia, schizoaffective disorder, major depression with psychotic symptoms, bipolar disorder, current anorexia, substance abuse or dependence and attention-deficit/hyperactivity disorder. Exclusion criteria for both patients and control participants were (1) dementia, cognitive impairment; (2) CNS relevant somatic diseases, neurological diseases, metabolic diseases (e.g., thyroid disease, diabetes), organic shift in cortisol secretion (e.g., Morbus Cushing), immune-mediated diseases, severe cardiovascular diseases, current infections; (3) use of beta-blockers, benzodiazepines or steroids; (4) pregnancy or nursing. These criteria were assessed by exhaustive anamnesis and an additional examination by a psychiatrist. Additionally, control participants were excluded if they had any former or current DSM-IV Axis I disorder. Psychiatric diagnoses were made by trained psychologists 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).

Healthy control participants were recruited by local advertising. They received financial remuneration for their efforts (100 €).

Written informed consent was obtained from all participants. The study was approved by the University of Muenster Ethics Committee and the Ethics Committee of the Medical Council of Hamburg.

2.2. Material

In order to test response inhibition, we administered an emotional go/no-go paradigm. The paradigm was obtained from a study by Hare et al. (2005) and extended by three emotional conditions to complete condition variability. The emotional go/no-go task consisted of human face stimuli with three different

emotional expressions (fearful, happy or neutral expression) selected from the NimStim Face Stimulus Set, Nim Tottenham, Sackler Institute, California (www.macbrain.org). We chose this paradigm, because it is known that occurrence of GC effects on cognition require adrenergic activation of the basolateral amygdala (Elzinga and Roelofs, 2005; Roozendaal et al., 2006) and human face stimuli were shown to reliably affect amydala activity (Hare et al., 2005). Moreover, the acute impact of cortisol on cognition has been found to be typically greater for emotionally arousing material than for neutral material (Buchanan and Lovallo, 2001; Abercrombie et al., 2006).

The stimuli showed full-color, open mouth facial expressions of 12 Caucasian adult individuals (6 females, 6 males) which were presented individually centered against a black background on a 21 inch computer screen (Eizo FlexScan ®F 730) using the software Presentation® (version 0.76, Neurobehavioral Systems Inc., SF, California). All images were normalized for size and luminance. After an initial practice block of 18 trials (12 go, 6 no-go), 6 experimental blocks each consisting of 36 trials (24 go, 12 no-go) were completed. In the practice block, facial expressions of disgust (go stimuli) and of surprise (no-go stimuli) were presented, while in the experimental blocks, fearful, happy and neutral facial expressions served as targets and non-targets. All blocks included only two categories of expressions, one target and one non-target, which were pseudo-randomized across the block to control for order of presentation. All combinations of expressions were used as both targets and non-targets and were presented to each participant in the following order: (1) fearful go/happy no-go; (2) happy go/neutral no-go, (3) neutral go/fearful no-go; (4) fearful go/neutral no-go; (5) neutral go/happy no-go; (6) happy go/fearful no-go. The duration of stimulus presentation was 500 ms, followed by an interstimulus interval (ISI) of 2000 ms (Fig. 1). Reaction times in milliseconds (ms) and number of errors of commission (response to no-go stimuli or 'false alarms') were recorded automatically.

2.3. Procedure

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. At the beginning of the go/no-go task, the examiner read aloud written instructions displayed on the computer screen. The instruction was as follows (first block of stimuli presentation, translated from German): 'You will now be presented different facial expressions, namely facial expressions, which are either *fearful* or *happy*. The facial expressions will be presented individually in the center of a black screen for a very short time. Please press the space key as fast as possible whenever you see a *fearful* facial expression and do not press when *happy* expressions are presented.' Additionally, participants were given examples of the two stimuli. At the start of each block, they received new instructions adapted to the different emotional stimuli (either fearful, happy or neutral) read aloud and presented on the screen and were reminded to respond as quickly and accurately as possible.

Each participant was tested twice after receiving either a dosage of 10 mg of hydrocortisone (Jenapharm®) or placebo (test–retest interval 5 to 7 days). The administration of hydrocortisone or placebo was randomized for the first testing session and counterbalanced for the second testing session. Randomization was carried out by a research assistant blind to the test administrators. Drugs were administered orally 45 min prior to testing, which took place between 1600 h and 1800 h. Neither test administrators nor patients knew which treatment was given (hydrocortisone or placebo) in the individual testing sessions. Saliva was collected 10 min before (baseline), 45 min (sample +45) and 90 min (sample +90) after cortisol or hydrocortisone administration, using saliva collection devices (Sarstedt AG, Nuembrecht, Germany). This timing procedure was chosen in accordance with our prior studies indicating high levels of cortisol 45 min after hydrocortisone administration and a decrease after 90 min (Schlosser et al., 2010; Terfehr et al., 2011a, 2011b). After being stored at room temperature until the session was completed the saliva was kept at −80 °C until the biochemical analysis. 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 analysis. Therefore, cortisol levels were only obtained from 36 patients and 27 control participants.

2.4. Statistical analysis

Demographic data were analyzed using chi-square tests for categorical data and Student's *t* tests for continuous data. Salivary cortisol was analyzed using analysis of variance (ANOVA) with

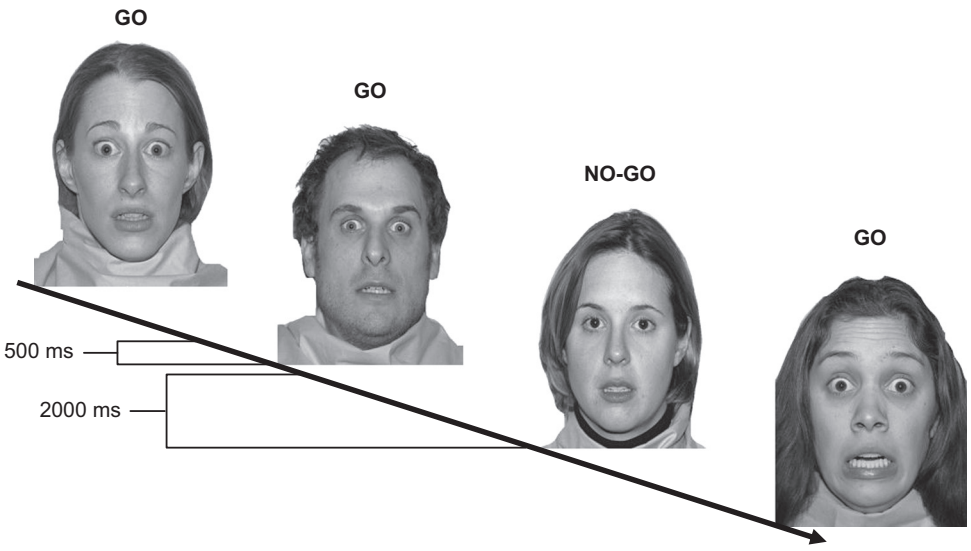

Fig. 1. Sample sequence of stimulus presentation in the go/no-go task (4th trial) with fearful expressions as targets and neutral expressions as non-targets (grey-scaled).

repeated measures with treatment (cortisol vs. placebo) and time (baseline, +45 min, +90 min) as the within-subjects factors and group (MDD vs. healthy control participants) as the between-subjects factor.

Regarding go/no-go performance, mean reaction times for correct responses to go-trials (positive: blocks 2 and 6; negative: blocks 1 and 4; neutral: blocks 3 and 5) and the mean number of false alarms (positive: blocks 1 and 5; negative: blocks 3 and 6; neutral: blocks 2 and 4) were calculated for each emotional condition (positive, negative, neutral). Effects of hydrocortisone on go/no-go performance were analyzed using a 2 (treatment: cortisol vs. placebo) × 3 (emotional condition: positive, negative, neutral) × 2 (group: patients vs. controls) factorial analysis of variance (ANOVA) with repeated measures. Reaction times and number of false alarms were defined as dependent variables and ANOVAs were conducted separately for each variable. Reaction times below 300 ms (anticipatory reaction) and above 1000 ms (delayed response) were defined as outliers and thus excluded from the analysis without replacement. Regarding errors of commission, no extreme outliers could be detected by SPSS outlier analysis. Concerning cortisol measures, two outliers in baseline cortisol levels could be identified by SPSS outlier analysis and were subsequently excluded from the initial sample, resulting in a final sample of 50 patients and 54 control participants. Given the well-established association of age with cognition in the existing literature, analysis of covariance (ANCOVA) with age as covariate was conducted. To analyze the effects of antidepressant medication and comorbid anxiety disorders, we conducted a separate ANOVA for the patients group only with status of medication and comorbid anxiety disorder as the between-subjects factors. We refrained from analyzing for type of medication due to small sample sizes. Bonferroni-adjusted post-hoc *t* tests were used in case of significant main effects. Level of significance was set to $P=0.05$ (two-sided tests) for all analyses. All statistical procedures were performed with the 'Statistical Package for the Social Sciences 14.0' (SPSS 14.0). Additionally, a post-hoc power analysis was conducted using the software G*Power 3 (Faul et al., 2007).

3. Results

3.1. Demographic and clinical data

MDD patients and healthy control participants did not differ concerning demographic variables (Table 1). As expected, patients were more depressed than control subjects according to the BDI (Table 1). 56% 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 23 weeks. 12 patients had one current comorbid diagnosis (social phobia $n=7$, specific phobia $n=2$, panic disorder $n=2$, eating disorders $n=1$). 38 patients were treated with antidepressant medication (selective serotonin reuptake inhibitors $n=17$, selective serotonin and norepinephrine reuptake inhibitors $n=15$, selective norepinephrine reuptake inhibitors $n=2$, selective noradrenalin and dopamine reuptake inhibitors $n=1$, tricyclics $n=2$, monoamine oxidase inhibitors $n=1$). All healthy participants were free of psychotropic medication.

3.2. Cortisol levels

Cortisol measurements could be conducted for 34 MDD patients and 27 healthy control participants (Fig. 2). A significant main effect of treatment could be revealed, reflecting increased saliva cortisol levels after administration of hydrocortisone compared to placebo ($F_{1,59}=97.869$, $P<0.001$). Furthermore, there was a significant time effect ($F_{2,118}=70.930$, $P<0.001$) as well as a significant treatment by time interaction ($F_{2,118}=68.309$, $P<0.001$). Post-hoc *t*-tests revealed significantly higher cortisol levels for hydrocortisone treatment compared to placebo treatment at baseline+45 min and baseline+90 min (all $P<0.001$), whereas cortisol levels at baseline did not differ between the two treatment conditions ($t_{64}=0.548$, $P=0.586$). There was neither a significant main effect of group ($F_{1,59}=0.187$, $P=0.667$), nor significant interaction effects with group.

To analyze the effects of antidepressant medication on cortisol levels, we conducted a separate ANOVA for the patients group only with status of medication as the between-subjects factor (25 medicated, 9 not medicated). There was no significant main effect of medication status on cortisol levels ($F_{1,32}=1.280$, $P=0.266$).

3.3. Response inhibition

With regard to reaction times (correct responses to targets), ANOVA indicated a significant group by treatment interaction ($F_{1,102}=4.628$, $P=0.034$) as well as significant main effects of target

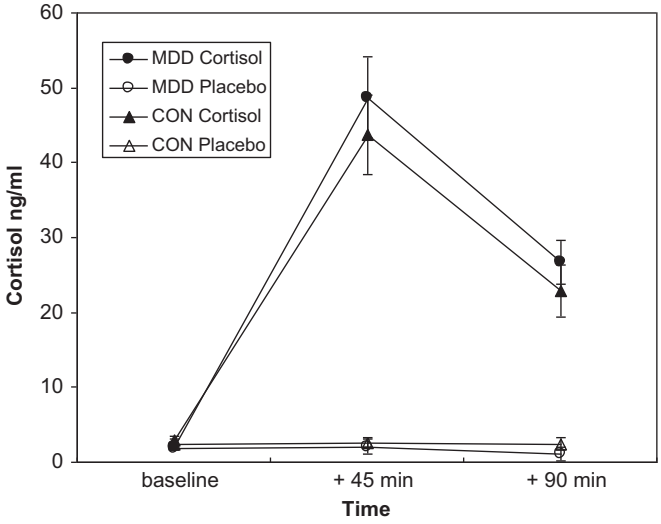

Fig. 2. Mean (SEM) saliva cortisol levels in patients with major depressive disorder (MDD, $n=34$) and healthy control participants (CON, $n=27$) after placebo and hydrocortisone administration.

Table 1
Demographic and clinical characteristics (means and standard deviations) of the sample ($N=104$).

Characteristics	MDD ($n=50$)	Controls ($n=54$)	Statistics
Age	34.34 (9.40)	31.46 (10.25)	$t_{102}=1.488$, $P=0.140$
Sex (male/female)	20/30	19/35	$\chi^2=0.257$, $P=0.612$
Years of formal school education	11.30 (1.46)	11.63 (1.52)	$t_{102}=-1.126$, $P=0.263$
BDI sum[a]	21.71 (11.11)	2.83 (3.60)	$t_{94}=10.585$, $P<0.001$

MDD=Major Depressive Disorder; BDI=Beck Depression Inventory.

[a] Data of 8 patients missing.

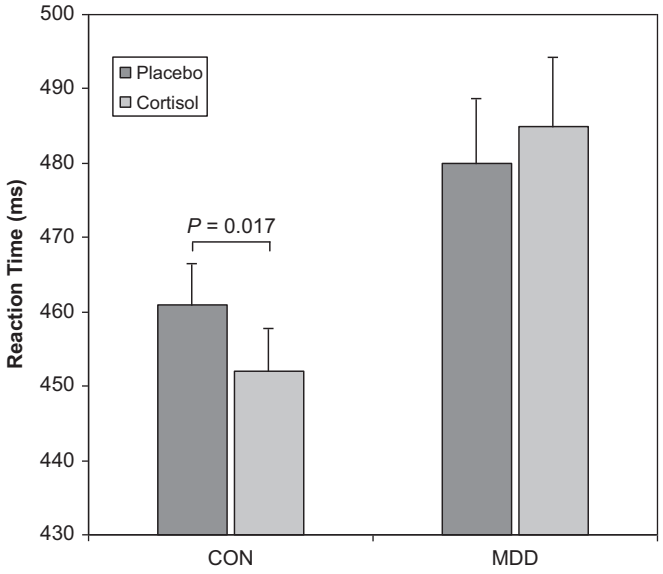

Fig. 3. Reaction times (mean, SEM) in patients with major depressive disorder (MDD, $n=50$) and healthy control participants (CON, $n=54$) after administration of 10 mg hydrocortisone or placebo in the go/no-go task.

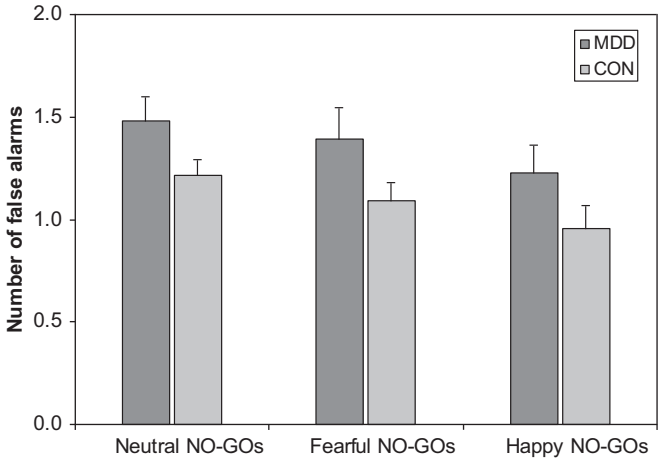

Fig. 4. Number of false alarms (mean, SEM) of patients with major depressive disorder (MDD, $n=50$) and healthy control participants (CON, $n=54$) in the emotional go/no-go task. Due to a missing treatment effect, data were averaged for both treatment conditions (hydrocortisone and placebo).

(go stimuli) emotion (neutral, fearful, or happy) ($F_{2,204}=106.357$, $P<0.001$) and group ($F_{1,102}=6.759$, $P=0.011$) with overall longer reaction times in the patients group ($M=482.34$, S.D.$=60.40$) compared to the control group ($M=456.58$, S.D.$=39.13$). No main effect of treatment ($F_{1,102}=0.419$, $P=0.519$) and no other interactions could be detected. Further analyzing the group by treatment interaction effect, post-hoc t tests with a Bonferroni corrected P-value of 0.05/2$=0.025$ revealed that healthy control participants responded significantly faster after cortisol administration ($M=452.05$, S.D.$=42.07$) compared to placebo treatment ($M=461.11$, S.D.$=40.70$; $t_{53}=-2.467$, $P=0.017$), while response times of MDD patients did not differ significantly between cortisol and placebo administration ($t_{49}=0.896$, $P=0.375$) (Fig. 3). Further analyzing the main effect of target emotion, post-hoc t tests with a Bonferroni corrected P-value of 0.05/3$=0.017$ revealed that responses were significantly slower when subjects hat to respond to neutral targets ($M=491.65$, S.D.$=59.04$) than when they had to respond to fearful ($M=467.71$, S.D.$=54.49$, $t_{103}=7.439$, $P<0.001$) or happy targets ($M=447.52$, S.D.$=50.61$, $t_{103}=14.459$, $P<0.001$). Additionally, reaction times for fearful targets were significantly longer compared to reaction times for happy targets ($t_{103}=7.322$, $P<0.001$). There were no significant differences in reaction times for patients and control participants between the first ($M=469.83$, S.D.$=54.25$) and the second test session ($M=470.70$, S.D.$=58.60$) ($F_{1,102}=0.039$, $P=0.843$). When controlling the analysis for age, we found a significant main effect of this covariate ($F_{1,101}=4.168$, $P=0.044$) on reaction times without any significant interaction effects, while the significant main effect of target emotion ($F_{2,202}=5.684$, $P=0.004$), group ($F_{1,101}=5.355$, $P=0.023$) and the significant interaction of group and treatment ($F_{1,101}=4.376$, $P=0.039$) remained stable. An analysis of a possible influence of antidepressant medication and comorbid anxiety disorder on reaction time analyzed by a separate ANOVA for the patients group did not reveal a significant main effect of medication ($F_{1,48}=0.799$, $P=0.376$) or comorbid anxiety disorder ($F_{1,48}=0.410$, $P=0.525$).

Concerning the number of false alarms (error responses to non-targets or errors of commission), ANOVA indicated a significant main effect of non-target (no-go stimuli) emotion (neutral, fearful, or happy) ($F_{2,204}=5.448$, $P=0.005$) and group ($F_{1,102}=4.273$, $P=0.041$) with more errors in the patients group ($M=1.37$, S.D.$=0.84$) compared to the control group ($M=1.09$, S.D.$=0.50$) (Fig. 4). No main effect of treatment ($F_{1,102}=0.090$, $P=0.765$) and no interactions could be detected. A post-hoc power analysis with an estimated effect size of Eta$^2=0.17$ (compare Scholz et al., 2009) revealed a power of 1.0 for our study. Further analyzing the main effect of non-target emotion, post-hoc t tests with a Bonferroni corrected P-value of 0.05/3$=0.017$ revealed a significantly higher number of false alarms when subjects were to inhibit neutral non-targets ($M=1.34$, S.D.$=0.71$) compared to inhibition of happy non-targets ($M=1.09$, S.D.$=0.87$, $t_{103}=3.441$, $P=0.001$). No significant differences in the number of false alarms between neutral and fearful non-targets ($M=1.24$, S.D.$=0.89$, $t_{103}=1.414$, $P=0.160$) as well as between fearful and happy non-targets ($t_{103}=1.824$, $P=0.071$) could be detected. Comparing the number of false alarms in the first and the second test session, ANOVA revealed a significant main effect of test session ($F_{1,102}=7.172$, $P=0.009$). Patients and control participants made significantly less errors in the second test session ($M=1.14$, S.D.$=0.83$) compared to the first test session ($M=1.31$, S.D.$=0.67$). When controlling the analysis for age, we did not find a significant effect of this covariate ($F_{1,101}=0.932$, $P=0.337$). Neither medication status ($F_{1,48}=0.071$, $P=0.791$) nor comorbid anxiety disorder ($F_{1,48}=1.832$, $P=0.182$) had a significant main effect on the number of false alarms, as indicated by a separately calculated ANOVA for the patients group only.

4. Discussion

This is the first study experimentally investigating the effects of acute cortisol administration on response inhibition in patients with MDD compared to healthy control participants.

Confirming our hypothesis, inhibitory performance regarding *reaction times* in the go/no-go task in patients with MDD was not affected through acute cortisol administration, while cortisol significantly affected reaction times in healthy control participants. The missing effect of acute cortisol administration in patients with MDD is in accordance with the results of prior studies of our working group where we found declarative, autobiographical and working memory not being affected by cortisol administration in patients with MDD while significantly being impaired in healthy control participants (Schlosser et al., 2010; Terfehr et al., 2011a, 2011b).This further supports the hypothesis of reduced central GC receptor function in patients with MDD (Schlosser et al., 2011).

Against our expectations, inhibitory performance regarding reaction times in healthy control participants was not impaired but improved after cortisol administration indicated by faster responses to go-stimuli in the go/no-go task. To our knowledge, only two studies of stress effects on inhibitory function included reaction times as a dependent variable. In accordance with our results, Oei et al. (2009) reported that healthy control participants receiving hydrocortisone (35 mg) by tendency responded faster in a Sternberg item-recognition task than participants receiving placebo. In contrast, Scholz et al. (2009) found reaction times in a go/no-go task to be slower in healthy participants stressed with a psychosocial stress induction compared to a non-stressed control group. From an evolutionary perspective, faster responses under stress as found in our study and in Oei et al. (2009) would make sense in respect of increasing the probability of survival. The available data, however, are to sparse to draw final conclusions and the stress effects on processing speed are in need of further clarification by future studies.

Furthermore, in contrast to our hypothesis, inhibitory performance regarding *errors of commission* was not affected by cortisol administration in healthy control participants. Our result of no impairment of inhibitory performance regarding errors of commission after acute cortisol administration in healthy control participants is consistent with Wolf et al. (2001), Oei et al. (2009) and Zwissler et al. (2011) who also found no impairing or even ameliorating effects of cortisol administration or psychosocial stress induction on inhibitory performance in healthy participants. Our findings contrast the results of Scholz et al. (2009), who found impairing effects on response inhibition in a go/no-go task after a psychosocial stress induction in healthy men. The inconsistency of results might best be explained by methodological differences, particularly treatment (cortisol administration vs. psychosocial stress induction), cortisol doses, time of testing (morning vs. afternoon) and usage of different tasks (SCWT, directed forgetting, go/no-go, Sternberg task).The fact that Scholz et al. (2009), in contrast to our study, found impairing effects of cortisol on inhibitory performance in a go/no-go task in healthy participants might result from differences in task load. Moreover, it might be that psychosocial stress (TSST) caused a higher arousal of participants than cortisol administration leading to concomitant activation of the adrenergic system, thus inducing a stronger impact on prefrontal cognitive function. Hydrocortisone administration and psychosocial stress induction also differ in a qualitative way as hydrocortisone only simulates an internal stress state by artificially raising cortisol levels on a physiological basis while a psychosocial stressor more adequately represents a real-life stressor including the psychological component of stress. In this regard, stressors characterized by uncontrollability and social-evaluative threat as in the TSST have been found to be associated with the largest cortisol responses (Dickerson and Kemeny, 2004). However, our intention was to avoid measuring other stress components than GCs (e.g. hormones of the adrenergic system) and therefore favored the administration of hydrocortisone. Our results also counter findings of pharmacological studies investigating the effect of hydrocortisone administration on prefrontal dependent WM (Lupien et al., 1999; Young et al., 1999; Wolf et al., 2001). In a recent placebo-controlled study from our group, working memory for negative stimuli was significantly impaired after hydrocortisone administration in healthy participants (Terfehr et al., 2011b). Impairing GC effects on WM have been replicated by studies using psychosocial stressors (Elzinga and Roelofs, 2005; Oei et al., 2006; Schoofs et al., 2008). However, some studies could not find an impairing effect of GC administration on WM performance (Monk and Nelson, 2002; Porter et al., 2002; Oei et al., 2009; Wingenfeld et al., 2011). All in all, these inconclusive results might be attributed to methodological differences, i.e. different doses and timing of GC administration or stress induction (acute vs. chronic, morning vs. afternoon), age and gender of participants, the selected stimuli (verbal vs. non-verbal, neutral vs. emotional) and different paradigms varying in sensitivity, in involvement of executive processes, and in executive demands.

Particularly, two methodological factors might have led to the missing cortisol effect on response inhibition (errors of commission) in healthy participants in the present study. The first is a possibly insufficient workload provided by the emotional go/no-go task. In this regard, it has repeatedly been demonstrated that effects of cortisol on working memory become apparent only in case of a high workload (Lupien et al., 1999; Langenecker et al., 2005; Oei et al., 2006; Schoofs et al., 2008). A higher workload could have been obtained by decreasing the probability of no-go stimuli (Robert and Pennington, 1996). Second, the emotional stimuli might have caused an insufficient arousal for cortisol effects to occur (Roozendaal et al., 2006). Thus, future studies should consider employing highly arousing stimuli.

Alternatively, it seems possible that inhibitory performance in general is less sensitive to changes induced by cortisol administration than working memory performance. Although both inhibition and working memory are mediated by the PFC, there might be differences in the activation of prefrontal subregions (e.g. DLPFC) and other brain structures (e.g. ACC) depending on the task employed and these subregions might be differentially affected by cortisol. Moreover, it has to be acknowledged that cortisol interacts with other neurotransmitter systems which exert influences on executive functions, particularly dopamine and norepinephrine (Arnsten and Li, 2005).

As expected, MDD patients performed more poorly in inhibitory control compared to non-depressed participants evidenced by significantly longer reaction times and more errors of commission. Thus, we confirmed earlier findings demonstrating inhibitory deficits indicated by slower reaction times and/or more errors of commission in patients with MDD using neutral (e.g. Schatzberg et al., 2000; Harvey et al., 2004; Gohier et al., 2009) or emotional stimuli (e.g. Goeleven et al., 2006; Lau et al., 2007; Beblo et al., 2010). In contrast to the latter studies, MDD patients and healthy control participants did not differ in their inhibitory performance depending on the emotionality of the stimuli, i.e. no interaction of emotional condition and group could be revealed. An explanation for the differing results could be that here we used fearful stimuli while the studies mentioned above used generally negative and more depression-related stimuli (e.g. sad facial expressions). As depression-related stimuli are assumed to be more salient to MDD patients than fearful stimuli, they probably elicit a stronger attentional bias resulting in reduced inhibition of such stimuli. The finding that both patients and healthy control participants demonstrated longer reaction times and more errors of commission to neutral facial expressions compared to fearful and happy expressions is somewhat surprising. Compared to prior studies investigating go/no-go performance with emotional and neutral stimuli and reporting significant effects of valence on reaction times or errors of commission, results are contradictory. Hare et al. (2005), from which we obtained our task, reported significantly longer reaction times to negative compared to neutral and positive stimuli, and more errors to positive compared to neutral and negative stimuli, contrasting our results. However, in line with our results, Elliott et al. (2000) found a trend for longer reaction times to neutral compared to sad and happy stimuli in a verbal go/no-go task in healthy participants, while no valence effect for errors emerged. In the present study, it might be that neutral facial expressions were the most ambiguous and thus the most difficult to recognize.

The present study has several limitations to be mentioned. The majority of patients in the present study were on antidepressant medication, which could have influenced HPA axis

function, GR sensitivity and inhibitory performance (Pariante et al., 2004; Schmitt et al., 2001). However, results of ANOVA did not indicate effects of medication neither on cortisol levels nor on inhibitory performance. In the future, studies investigating the effects of hydrocortisone on response inhibition in medication free patients are warranted. One could argue that the slowed responses of MDD patients in our study might not result from inhibitory deficits but from a lack of motivation. However, it has repeatedly been observed that depressed patients are highly motivated when performing neuropsychological testing (Beblo et al., 2011), so motivation deficits unlikely account for response slowing in the present study. Moreover, we did not assess subjective and arousal ratings of the stimuli used in this study. Thus, we cannot determine whether the negative stimuli would have been rated as more arousing than the neutral ones or whether patients and controls would have differed in their ratings. We can also not rule out that inhibitory performance in MDD patients might have been influenced by disturbances in face emotion perception; e.g. MDD patients have been shown to interpret emotionally neutral faces as sad and to be impaired in disengaging attention from sad faces (Leppänen, 2006). However, Langenecker et al. (2005) demonstrated that accuracy of face emotion perception was not related to inhibitory control in a go/no-go task in depressed women. Finally, a learning effect as indicated by less errors of commission in the second test session compared to the first one for all participants could have covered treatment effects. A strength of the present study is the large sample size, thus lack of statistical power as a possible explanation for missing treatment effects seems unlikely, which was confirmed by a post-hoc power analysis.

In conclusion, the present study lends further support to the hypothesis of impaired central GC receptor function in patients with MDD and replicates findings of impaired inhibitory control in patients with MDD. Inhibitory impairments adversely impact upon MDD patients' abilities to cope with the demands of daily functioning. In this respect, there is a need for further examination of GC effects on response inhibition in depressed patients and healthy control participants. These studies should include a multidimensional (baseline function and function after pharmacological and psychosocial stress provocation) and multimethodological assessment (e.g. dexamethasone-suppression-test, prednisolone test) of HPA axis function as well as sensitive measures of inhibitory control considering the employment of high workload tasks and of high arousing stimuli.

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