Mineralocorticoid Receptor Stimulation Improves Cognitive Function and Decreases Cortisol Secretion in Depressed Patients and Healthy Individuals

Christian Otte*,[1], Katja Wingenfeld[1], Linn K Kuehl[1], Michael Kaczmarczyk[1], Steffen Richter[1], Arnim Quante[1], Francesca Regen[1], Malek Bajbouj[1], Frank Zimmermann-Viehoff[1], Klaus Wiedemann[2] and Kim Hinkelmann[1]

[1]Department of Psychiatry and Psychotherapy, Charité University Medical Center, Campus Benjamin Franklin, Berlin, Germany; [2]Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Memory and executive function are often impaired in patients with major depression, while cortisol secretion is increased. Mineralocorticoid receptors (MR) are abundantly expressed in the hippocampus and in the prefrontal cortex, brain areas critical for memory, executive function, and cortisol inhibition. Here, we investigated whether MR stimulation with fludrocortisone (1) improves memory and executive function and (2) decreases cortisol secretion in depressed patients and healthy individuals. Twenty-four depressed patients without medication and 24 age-, sex-, and education-matched healthy participants received fludrocortisone (0.4 mg) or placebo in a randomized, double-blind, within-subject cross-over design. We measured verbal memory, visuospatial memory, executive function, psychomotor speed, and salivary cortisol secretion during cognitive testing between 1400 and 1700 hours. For verbal memory and executive function, we found better performance after fludrocortisone compared with placebo across groups. No treatment effect on other cognitive domains emerged. Depressed patients performed worse than healthy individuals in psychomotor speed and executive function. No group effect or group × treatment interaction emerged on other cognitive domains. Fludrocortisone decreased cortisol secretion across groups and there was a significant correlation between cortisol inhibition and verbal memory performance. Our data suggest a crucial role of MR in verbal memory and executive function and demonstrate the possibility to improve cognition in depressed patients and healthy individuals through MR stimulation.

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INTRODUCTION

Patients with major depression often exhibit cognitive deficits. Memory and executive function are among those domains that are most consistently impaired in depressed patients. Importantly, several groups have found impaired memory and executive function to be associated with elevated cortisol in patients with major depression (Behnken *et al*, 2013; Gomez *et al*, 2006; Hinkelmann *et al*, 2009, 2013; O'Hara *et al*, 2007) although not all studies concur (Krogh *et al*, 2012).

Cortisol exerts its effects in the brain via two different nuclear receptors, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). GR are distributed throughout the brain and have a low affinity for cortisol, whereas MR have a high cortisol affinity and are expressed primarily in limbic areas. Both receptors are abundantly expressed in the hippocampus and in the prefrontal cortex, brain areas critical for memory and executive function (Rock *et al*, 2013; Trivedi and Greer, 2014; Wagner *et al*, 2012). Lately, animal and human studies have revealed the existence of a membrane-bound MR-mediating rapid non-genomic effects with an intermediate cortisol affinity (Henckens *et al*, 2011; Joels *et al*, 2013; van Ast *et al*, 2013). Both GR and MR inhibit cortisol secretion through negative feedback inhibition (de Kloet, 2013). Although GR alterations leading to high cortisol and impaired cognitive function have been consistently described in major depression (Herbert, 2013; Pariante and Lightman, 2008), much less is known about the role of MR in cortisol secretion and cognitive function.

Animal studies have consistently shown a role for the MR in cortisol secretion and memory performance and executive function (Joels *et al*, 2008). For example, blockade of MR impairs spatial memory (Berger *et al*, 2006; Brinks *et al*, 2009; Qiu *et al*, 2010; ter Horst *et al*, 2012), and working memory (Berger *et al*, 2006). In contrast, the overexpression of MR has been consistently associated with improved memory in animals (Ferguson and Sapolsky, 2008; Harris *et al*, 2013; Lai *et al*, 2007; Rozeboom *et al*, 2007). In healthy

*Correspondence: Professor C Otte, Department of Psychiatry and Psychotherapy, Charité University Medical Center, Campus Benjamin Franklin, 14050 Berlin, Germany, Tel: +49 30 8445 8253, Fax: +49 30 8445 8255, E-mail: christian.otte@charite.de

humans, blockade of the MR impaired memory and executive function in young healthy men and increased cortisol secretion (Cornelisse et al, 2011; Otte et al, 2007; Rimmele et al, 2013). Furthermore, MR stimulation with the agonist fludrocortisone inhibits cortisol secretion in humans (Buckley et al, 2007; Otte et al, 2003, 2010a). However, this inhibition is attenuated in patients with psychotic depression suggesting impaired MR function in these patients (Lembke et al, 2013). Importantly, psychotically depressed patients show the most severe cognitive deficits (Schatzberg et al, 2000). Furthermore, there is evidence of decreased MR expression in the hippocampus and prefrontal cortex in depressed patients (Klok et al, 2011a; Medina et al, 2013). Finally, GR blockade with mifepristone improved cognitive function in bipolar depressed patients and the authors speculated that this might be due to an increased MR-mediated signal (Watson et al, 2012).

In sum, there is a plethora of data suggesting an important role of MR function on cognition in healthy individuals (Joëls et al, 2008) and first evidence of impaired MR function in major depression (Klok et al, 2011a; Medina et al, 2013). However, so far no study directly examined a potential therapeutic effect of MR stimulation, neither in healthy individuals nor in depressed patients. Therefore, we examined the acute effects of the MR agonist fludrocortisone on memory and executive function as well as cortisol secretion in depressed patients and age-, sex-, and education-matched healthy controls. We hypothesized that, in both groups, fludrocortisone would improve memory and executive function and decrease cortisol secretion.

PATIENTS AND METHODS

Participants

We recruited 24 unmedicated depressed patients according to DSM-IV criteria from a specialized depression clinic at the Department of Psychiatry and Psychotherapy, Charité University Medical School, Berlin. Inclusion criteria were (1) a diagnosis of major depressive disorder, single, or recurrent according to DSM-IV criteria; (2) a minimum baseline score of 18 points on the Hamilton Rating Scale for Depression, 17-item version (HDRS-17); (3) age from 18 to 40 years; and (4) a period of at least 3 days free from antidepressants, antipsychotics, mood stabilizers, and other medications influencing HPA activity. Only sleep medication and benzodiazepines as needed were allowed and only three patients used sleep medication or benzodiazepines during the days of testing. About half of the patients refered were first-episode patients and therefore drug naïve. The remaining patients were referred either untreated or with major depression despite medication. The latter group went through a 3-day washout and was switched to a different medication immediately after the examination. No patient experienced discontinuation symptoms from cessation of medication.

Criteria for exclusion were (1) dementia, schizophrenia spectrum disorder, bipolar disorder, substance dependence within the last 6 months according to the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al, 1998); (2) serious medical conditions, especially those associated with adrenal dysfunctions, steroid use, or well-known impact on HPA activity (eg, diabetes mellitus) or cognitive function; (3) pregnancy and nursing; and (4) fluoxetine medication due to long half-life time.

A control group of 24 healthy subjects recruited by public postings and matched for age, sex, and years of education were enrolled in the study. Healthy subjects were free of former and present DSM-IV Axis I disorders according to the MINI, had no physical illness, and had been free of any medication at least 3 months. In patients and healthy individuals, depressive symptoms were assessed by the self-report Beck Depression Inventory. The HDRS-17 as clinical interview was only applied in patients.

All participants underwent a screening procedure consisting of a medical and psychiatric history questionnaire (evaluating current lifetime psychiatric diagnosis and medical history, use of medication, alcohol, substance abuse, and smoking), and a routine medical examination. The study was approved by the local ethics committee. After complete description of the study to the subjects, written informed consent was obtained.

Procedures

Participants ingested four fludrocortisone (0.1 mg each) pills (Astonin H, Merck Serono GmbH, Germany) or four identical looking placebo pills in a randomized order and a double-blind, cross-over design with 3 days in between test days. The order of fludrocortisone and placebo administration was balanced. All subjects were tested in the afternoon between 1400 and 1700 hours with fludrocortisone being administered at 1400 hours. After a 90-minute break following drug administration, participants underwent cognitive testing. Blood pressure was assessed at 1400 hours (baseline), 1600, and 17:00 hours by an automatic device (Carescape V100, GE Healthcare). Salivary cortisol was collected during cognitive testing between 1400 and 1700 hours. Specifically, baseline samples were taken at 1350 and 1400 before medication intake. Afterward, samples were taken between 1500 and 1700 hours every half an hour. All samples were taken while study personnel were present. All participants received oral and written instructions on the correct use of the Salivette salivary collection device (Sarstedt AG, Nümbrecht, Germany).

Neuropsychological Assessment

Rey–Osterrieth complex figure test and Taylor complex figure test. These tests measure visuospatial memory (Osterrieth, 1944). The participant is first required to copy a complex figure. Immediately thereafter (direct recall) and 20 min later (delayed recall) the figure has to be re-drawn from memory.

Auditory verbal learning test. The auditory verbal learning test (AVLT) is a measure of short-term and long-term verbal memory (Lezak, 1995). The experimenter reads a list of 15 words (list A), which the participant is requested to repeat in loose order. After list A has been presented five times, the subject is asked to reproduce words from a newly presented list (list B). Following this, the subject is instructed to recall the words from list A without renewed presentation. After 30 min, the subject is again asked to repeat the words from list A (delayed recall).

Trail making test. Psychomotor speed was assessed with the trail making test (TMT) part A (Reitan, 1992). In this task, the subject has to connect encircled numbers in ascending order as quickly as possible. Part B assesses aspects of executive function, ie, cognitive set shifting and requires the alternation between numbers and letters, again in ascending order.

Hormonal Assessment

Cortisol was determined by radioimmunoassay (DRG, Marburg, Germany). Interassay and intra-assay coefficients of variation were below 8% and the detection limit was 0.5 ng/ml.

Statistical Analyses

Demographic characteristics between depressed patients and healthy participants were compared using *t*-tests for continuous variables and χ^2-tests for dichotomous variables. Separate (rm-ANOVA) with treatment (fludrocortisone *vs* placebo) as within-subject factor and group (depressed patients *vs* healthy controls) as between-subject factor were conducted to examine differences in blood pressure, memory, executive function, and cortisol secretion. We also calculated cortisol delta values (highest baseline value minus lowest value after placebo or fludrocortisone ingestion) for each condition. For all participants, the single lowest cortisol value was found during the last three measurement time points.

RESULTS

There were no significant differences between depressed patients and healthy controls on demographic variables. Information on demographic variables is given in Table 1.

Psychomotor Speed: TMT A

For psychomotor speed as dependent variable, rm-ANOVA with treatment (fludrocortisone *vs* placebo) as within-subject factor and group (depressed *vs* healthy controls) as

between-subject factor did not reveal a significant treatment effect (F = 0.1, *p* = 0.96) but a significant group effect (F = 6.6, *p* = 0.01) indicating slower psychomotor speed in depressed patients compared with healthy controls. There was no group × treatment interaction (F = 0.05, *p* = 0.83).

Executive Function: TMT B

To obtain a measure of executive function not influenced by psychomotor speed, we defined executive function as time TMT B minus time TMT A. Rm-ANOVA with treatment (fludrocortisone *vs* placebo) as within-subject factor and group (depressed patients *vs* healthy controls) as between-subject factor revealed a significant treatment effect (F = 4.4, *p* = 0.04) indicating improved executive function after fludrocortisone across groups. As can be seen in Figure 1, the effects were much stronger in depressed patients that in healthy controls. Therefore, we conducted exploratory *post hoc* tests that confirmed significant treatment effects in the depressed patients (F = 5.2, *p* = 0.03, effect size partial η^2: 0.18) but failed to find significant treatment effects in healthy individuals (F = 0.35, *p* = 0.56).

The group effect was not significant (F = 1.4, *p* = 0.24). There was no group × treatment interaction (F = 1.0, *p* = 0.32).

Verbal Memory: AVLT

Rm-ANOVA with treatment (fludrocortisone *vs* placebo) as within-subject factor and group (depressed patients *vs* healthy controls) as between-subject factor revealed a significant treatment effect for AVLT delayed recall (F = 4.9, *p* = 0.03), indicating better verbal memory delayed recall in the fludrocortisone condition compared with placebo across groups. As can be seen in Figure 2, the effects were much stronger in depressed patients that in healthy controls. Therefore, we conducted exploratory *post hoc* tests that confirmed significant treatment effects in the depressed patients (F = 4.2, *p* = 0.05, effect size partial η^2: 0.15) but failed to find significant treatment effects in healthy individuals (F = 0.36, *p* = 0.55). There was neither a group

Table 1 Demographic and Clinical Variables

	Depressed patients N = 24	Healthy controls N = 24	
Mean age	26.5 ± 3.1	26.8 ± 3.5	NS
Sex, % females	70.8	70.8	NS
Smoker, %	41.6	29.6	NS
Education, years	12.0	12.1	NS
Body mass index	23.3	23.2	NS
BDI, mean	31.8 ± 7.6	3.3 ± 2.6	*p* < 0.001
HDRS-17, mean	24.8 ± 4.8	—	—

Abbreviations: BDI, Beck Depression Inventory; HDRS-17, Hamilton Depression Rating Scale − 17-item version; NS, not significant.
Comparisons between depressed patients and healthy controls based on one-way ANOVA for continuous variables and χ^2-test for dichotomous variables.
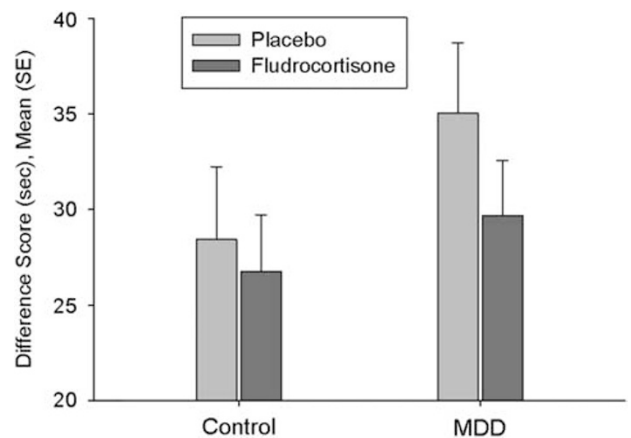

Figure 1 Executive function as measured by Trail Making Test B minus Trail making test A in seconds; treatment effect: *p* = 0.04, group × treatment: *p* = NS, group effect *p* = NS.

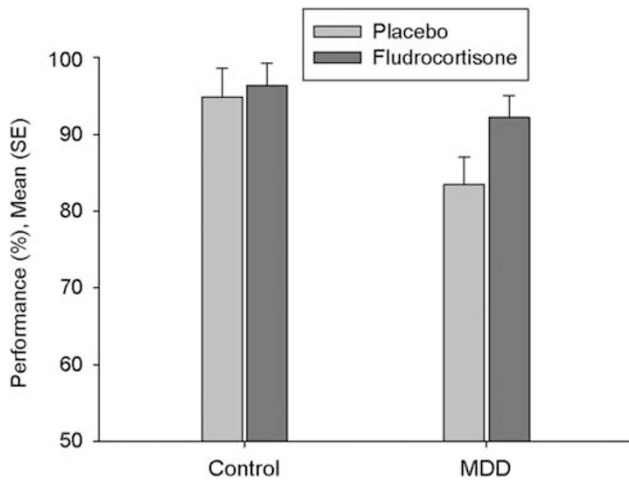Figure 2 Verbal learning memory test; % correct answers in delayed recall; treatment effect: $p = 0.03$, group × treatment: $p = $ NS, group effect $p = $ NS.

effect (F = 2.6, $p = 0.11$) nor a treatment by group interaction (F = 1.8, $p = 0.18$).

With regard to the learning curve of the presented words during the five trials, there was no treatment effect (F = 0.30, $p = 0.59$) and no treatment × group interaction (F = 0.21, $p = 0.65$) but a significant group effect indicating impaired learning in depressed patients vs healthy controls (F = 5.1, $p = 0.03$).

Visuo Spatial Memory: Rey/Taylor Figure

Rm-ANOVA with time (copy, direct recall, delayed recall) and treatment (fludrocortisone vs placebo) as within-subject factor and group (depressed patients vs healthy controls) as between-subject factor did not reveal a significant treatment effect (F = 0.4, $p = 0.52$), or group effect (F = 2.6, $p = 0.11$), or treatment × group interaction (F = 1.4, $p = 0.24$).

Cortisol Secretion During Cognitive Testing

Rm-ANOVA with time (seven time points) and treatment (fludrocortisone vs placebo) as within-subject factor and group (depressed patients vs healthy controls) as between-subject factor revealed no significant treatment effect, group effect or group × treatment interaction. However, a significant treatment × time interaction (F = 9.5, $p < 0.01$) indicated stronger cortisol suppression after fludrocortisone compared with placebo (Figure 3). These results were corroborated by analyses using delta values, for which we found in ANOVA a significant treatment effect (F = 8.2, $p < 0.01$), again suggesting greater cortisol suppression after fludrocortisone compared with placebo. No group effect (F = 0.2, $p = 0.88$) or group × treatment interaction (F = 0.8, $p = 0.38$) emerged for delta values.

Correlation between Cortisol Suppression after Fludrocortisone and Cognitive Performance

We found a strong correlation ($r = 0.45$, $p < 0.01$) between cortisol suppression after fludrocortisone (delta value) and
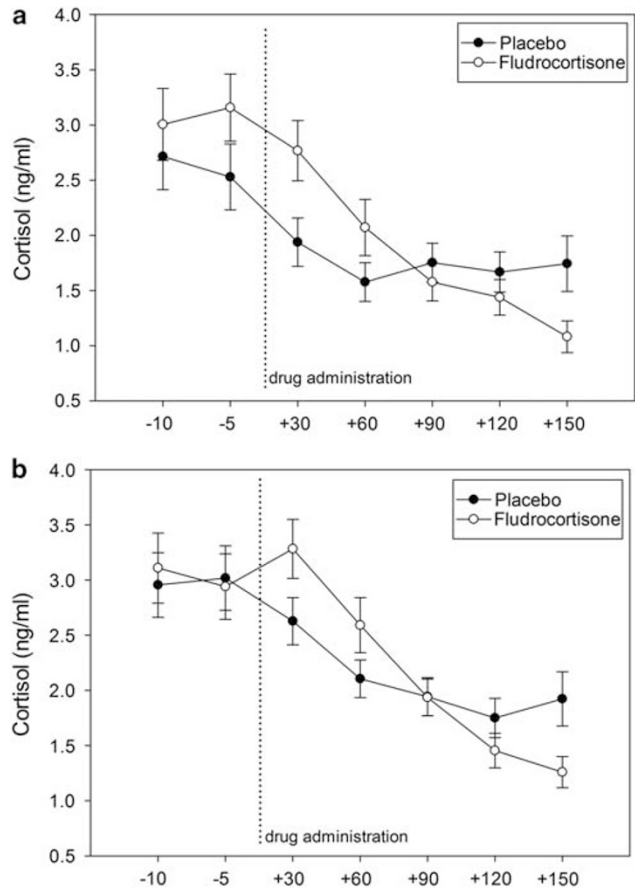

Figure 3 Cortisol secretion after placebo and fludrocortisone; a significant treatment × time interaction (F = 9.5, $p < 0.01$) indicates stronger cortisol suppression after fludrocortisone compared with placebo across groups; (a) healthy controls, (b) depressed patients.

verbal memory retrieval as expressed in percentage of correctly identified items in the delayed recall task of the AVLT (Figure 4). However, no significant correlation between cortisol suppression after fludrocortisone and executive function or visuospatial memory emerged.

Blood Pressure

There was no significant effect of treatment indicating that fludrocortisone did not increase diastolic (F = 0.19, $p = 0.66$) or systolic (F = 0.02, $p = 0.88$) blood pressure. Furthermore, there was no group effect indicating that depressed patients did not differ in diastolic (F = 1.1, $p = 0.29$) or systolic (F = 0.73, $p = 0.39$) blood pressure values from healthy controls. Finally, we found no group × treatment interaction on diastolic (F = 0.24, $p = 0.62$) or systolic (F = 0.19, $p = 0.66$) blood pressure.

DISCUSSION

We examined the effect of the MR agonist fludrocortisone on memory, executive function, and cortisol secretion in medication-free depressed patients and age-, sex-, and
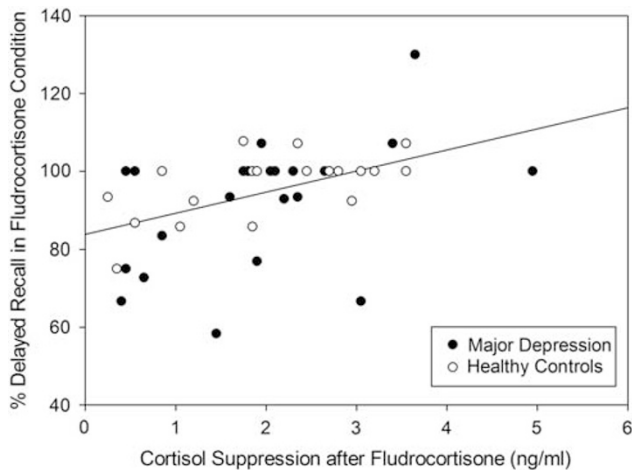
Figure 4 Correlation between cortisol suppression after fludrocortisone and percentage of correct answers in delayed recall of verbal memory in the fludrocortisone condition (across groups: $r = 0.45$, $p < 0.01$; healthy controls: $r = 0.60$, $p < 0.01$; depressed patients: $r = 0.41$, $p = 0.059$).

education-matched healthy participants. We found significantly improved verbal memory and executive function across groups after fludrocortisone compared with placebo. Furthermore, fludrocortisone inhibited cortisol secretion across groups. The magnitude of cortisol suppression after fludrocortisone was strongly associated with verbal memory performance.

Our data suggest that it is possible to acutely improve memory and executive function in depressed patients through MR stimulation. This is biologically plausible because MR expression is highest in the hippocampus and prefrontal cortex, two brain areas crucial for memory and executive function. Of note, memory and executive function are among those domains that are most consistently impaired in depressed patients (Rock et al, 2013; Wagner et al, 2012). Indeed, it has been repeatedly shown that depressed patients exhibit decreased MR expression in hippocampus and prefrontal cortex in post-mortem studies (Klok et al, 2011a; Medina et al, 2013; Qi et al, 2013). Furthermore, polymorphisms and haplotypes of the MR gene have been shown to be associated with depression (Klok et al, 2011b) and to moderate the association between childhood neglect and amygdala reactivity (Bogdan et al, 2012). Also, there was an attenuated cortisol inhibition in psychotic major depression after fludrocortisone also consistent with impaired MR function in these patients (Juruena et al, 2013; Lembke et al, 2013). Indeed, a potentially beneficial effect of fludrocortisone in the treatment of depressed patients was already suggested in a previous study, in which we demonstrated that add-on MR stimulation accelerates the treatment response to standard antidepressants (Otte et al, 2010b). In sum, there is accumulating evidence that MR alteration have a crucial role in major depression. This study extends these findings and suggests that MR stimulation might be a novel therapeutic approach to improve cognitive function and to decrease cortisol secretion in depressed patients.

However, in our current study, we did not find impaired cortisol suppression after fludrocortisone administration in depressed patients compared with healthy controls. This would suggest intact MR function in our depressed patients, as opposed to the well-known GR alterations in depression (Herbert, 2013; Pariante and Lightman, 2008). This is in line with an endocrine study in 12 depressed outpatients that found rather enhanced in contrast to impaired MR function in depressed outpatients (Young et al, 2003). Interestingly, one previous study showed MR alterations in psychotically depressed patients but not in patients with non-psychotic depression (Lembke et al, 2013). Furthermore, impaired MR-mediated cortisol inhibition prospectively predicted treatment resistance in depressed patients (Juruena et al, 2009). It is possible, therefore, that impaired MR function indicates a more severe course of depression but is not necessarily present in patients with non-psychotic depression or without a history of treatment resistance.

Our results concur with recent results from human studies showing that blockade of MR impairs memory function in young healthy men (Cornelisse et al, 2011; Otte et al, 2007; Rimmele et al, 2013). Our findings are also compatible with a recent study demonstrating that predominant MR activation benefits declarative memory consolidation during sleep (Groch et al, 2013). Finally, animal studies have consistently shown that MR over-expression enhances memory (Ferguson and Sapolsky, 2008; Harris et al, 2013; Lai et al, 2007), that MR stimulation enhanced long-term potentiation (Maggio and Segal, 2007), and that reduced hippocampal MR expression is associated with spatial memory impairment (Berger et al, 2006; Brinks et al, 2009; Qiu et al, 2010; ter Horst et al, 2012) and working memory deficits (Berger et al, 2006). Furthermore, the GR antagonist mifepristone antagonist was associated with an increase in cortisol awakening response and with a sustained improvement in spatial working memory performance (Watson et al, 2012). Interestingly, the magnitude of this neuropsychological response was predicted by the magnitude of the cortisol response to mifepristone. The results of that study are compatible with the idea that increased MR signaling in the face of GR blockade is responsible for improved spatial working memory. However, in our study, we used the Rey-Figure that measures immediate and delayed retrieval of visuospatial memory as opposed to spatial working memory. This might at least in part explain why we did not find effects on visuospatial memory. In summary, both animal and human data have now clearly proven an important role of MR function in cognition and our study suggests that it is possible to acutely improve cognition through MR stimulation.

What might be the mechanisms by which MR stimulation improves verbal memory and executive function? In addition to classical intracellular MR, membrane-bound MR that mediate rapid non-genomic effects have consistently been described (Joels et al, 2008, 2012, 2013). Membrane-bound MR are involved in fast cognitive effects (Khaksari et al, 2007; Schwabe et al, 2010) by promoting glutamate release in the hippocampus and prefrontal cortex (Joels et al, 2008). Therefore, this is a plausible pathway of fludrocortisone-associated effects on memory and executive function. Furthermore, stimulation of MR inhibits the release of corticotropin-releasing factor (CRF; Muller et al, 2003),

which in turn is associated with stress-associated cognitive deficits (Wang et al, 2011) and which is increased in patients with major depression (Binder and Nemeroff, 2010; Gold and Chrousos, 2013; Holsboer and Ising, 2010). Therefore, it is possible that CRF inhibition and consecutive lower cortisol values after MR stimulation leads to improved cognitive function. Furthermore, fludrocortisone has some glucocorticoid potency in addition to its mineralocorticoid activity although its MR affinity is about 150 times higher than its GR affinity (Agarwal et al, 1977). The extent of its glucocorticoid potency ranges from negligible to rather moderate depending on the source of the literature and variable being examined (Grossmann, 2004; Miller, 2008). In any event, remaining GR activity could also contribute to the effects of fludrocortisone.

Our study had several strengths. We included a relatively young and homogenous group of depressed patients without current antidepressants, mood stabilizer, or antipsychotics. Furthermore, healthy control participants were carefully matched for age, sex, and education. We measured salivary cortisol parallel to cognitive testing to relate cognitive performance to cortisol secretion during testing. However, several limitations have to be kept in mind when appraising our findings. First, we administered fludrocortisone only once and it is not clear if a longer-term fludrocortisone treatment will exert beneficial effects on memory and executive function. Furthermore, potential side effects need to be considered when weighing potential benefits and risks of fludrocortisone administration. However, this one-time administration of fludrocortisone did not exert any effects on blood pressure in neither of the groups. In the depressed group, 60 min after fludrocortisone administration, there was a slight cortisol increase before fludrocortisone-mediated cortisol inhibition. Therefore, we cannot completely rule out cross-reactivity between cortisol and fludrocortisone in the laboratory assays. However, this increase was not present in healthy individuals making cross-reactivity less likely. Furthermore, in both groups, cortisol continued to fall after fludrocortisone administration until the last measurement time point and it is possible that between-group differences would have been more pronounced in the later stages of cortisol inhibition after fludrocortisone. Therefore, future studies should measure cortisol for a longer time after fludrocortisone to ensure that complete cortisol suppression is captured. Finally, in our design, we were not able to clearly distinguish between fludrocortisone effects on memory acquisition, consolidation, and retrieval. This is important because in the case of hydrocortisone it has clearly been shown that it enhances memory consolidation but impairs memory retrieval in healthy subjects (Wingenfeld and Wolf, 2011). However, our results indicate that the net effect of fludrocortisone was beneficial on verbal memory as well as on executive function.

In summary, we found beneficial effects of the MR agonist fludrocortisone on verbal memory and executive function in depressed patients and healthy controls. Furthermore, in a recent study, we found beneficial effects of fludrocortisone on empathy in patients with Borderline personality disorder (Wingenfeld et al, 2014). Therefore, stimulating the MR appears to be a new opportunity for cognitive enhancement in health and disease.

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