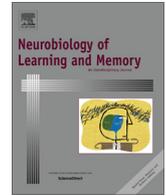




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# Neurobiology of Learning and Memory

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## Effects of mineralocorticoid receptor stimulation via fludrocortisone on memory in women with borderline personality disorder



Katja Wingenfeld\*, Linn K. Kuehl, Katrin Janke, Kim Hinkelmann, Franciska C. Eckert, Stefan Roepke<sup>1</sup>, Christian Otte<sup>1</sup>

Department of Psychiatry, Charité University Berlin, Campus Benjamin Franklin, Berlin, Germany

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### ABSTRACT

In a previous study, we found that in contrast to healthy controls, hydrocortisone administration had enhancing effects on memory in patients with borderline personality disorder (BPD). Because hydrocortisone acts on glucocorticoid receptors (GR) and mineralocorticoid receptors (MR), it is unclear which receptor mediated these effects. The aim of the current study was to test whether more selective MR stimulation with fludrocortisone improves memory in BPD.

In a placebo-controlled, randomized, within-subject, cross-over study, 39 medication-free women with BPD and 39 healthy women received placebo or 0.4 mg fludrocortisone prior to cognitive testing. We measured verbal memory, visuospatial memory, and working memory.

We found a significant group by fludrocortisone interaction on verbal memory and visuospatial memory. In both tests patients with BPD, but not healthy women, had impaired memory performance after fludrocortisone compared to placebo. In contrast, working memory was improved after fludrocortisone compared to placebo in both groups.

Contrary to our hypothesis, we found impairing effects of MR stimulation on hippocampus-mediated verbal memory and visuospatial memory in BPD but not in healthy controls. In contrast, working memory, which depends more on the prefrontal cortex, was improved after MR stimulation across groups. Future studies should systematically disentangle beneficial and adverse effects of MR stimulation in health and disease.

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### 1. Introduction

Glucocorticoids (GC), i.e., cortisol in humans, influence a wide range of cognitive functions, including declarative memory performance and working memory. Cortisol binds to two subtypes of intracellular and membrane-bound receptors, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR), which differ in their affinity to cortisol and distribution within the brain (de Kloet, 2013). While most of the effects of GCs have been attributed to GR function, more recent studies emphasize the importance of the MR (de Kloet, 2010, 2013; Harris, Holmes, de Kloet, Chapman, & Seckl, 2012; Joels, Karst, DeRijk, & de Kloet, 2008). For instance, blocking the MR leads to impaired cognitive function in healthy individuals (Cornelisse, Joels, & Smeets, 2011; Otte et al., 2007; Rimmele, Besedovsky, Lange, & Born, 2013).

\* Corresponding author at: Department of Psychiatry and Psychotherapy, Charité University Berlin, Campus Benjamin Franklin, Eschenallee 3, 14050 Berlin, Germany. Fax: +49 30 8445 8255.

E-mail address: [katja.wingenfeld@charite.de](mailto:katja.wingenfeld@charite.de) (K. Wingenfeld).

<sup>1</sup> Christian Otte and Stefan Roepke share the last authorship.

Accordingly, further studies examined whether stimulating the MR might in turn improve cognition. Indeed, MR stimulation with the agonist fludrocortisone not only inhibits cortisol secretion in humans (Buckley, Mullen, & Schatzberg, 2007; Otte et al., 2010) but also improves sleep-dependent memory consolidation (Groch, Wilhelm, Diekelmann, & Born, 2013). Furthermore, we recently found that fludrocortisone improves performance in a wide range of neuropsychological tests, including verbal memory, visuospatial memory and executive function in healthy individuals and depressed patients (Hinkelmann, Wingenfeld, Kuehl, Fleischer, & Otte, 2015; Otte et al., 2014).

However, in patients with borderline personality disorder (BPD), the effects of glucocorticoids on cognitive function have received little attention. In a recent study, we found that administration of hydrocortisone had enhancing effects on memory retrieval of words, on autobiographical memory, and on working memory in BPD patients while healthy controls showed impaired memory performance (Wingenfeld et al., 2013). However, as hydrocortisone stimulates both the GR and the MR, it remains unclear whether this effect is due to GR or MR

stimulation. Thus, it is possible that the positive effects of hydrocortisone on memory in BPD are also MR mediated.

In order to examine MR functioning in BPD, we administered fludrocortisone to stimulate the MR in patients with BPD and healthy controls and measured its effects on social cognition. Interestingly, we found higher scores on emotional empathy after fludrocortisone compared to placebo in healthy participants as well as patients with BPD, while there was no effect on cognitive empathy (Wingenfeld et al., 2014). These first results suggest unaltered MR functioning in BPD. Accordingly, a recent study of our group measured steroid sensitivity, i.e., ability of corticosteroids to inhibit T cell proliferation and did not find any differences between BPD patients and controls in MR and GR sensitivity (Fischer, Grundmann, Gold, Spitzer, & Wingenfeld, 2014). However, other studies suggest dysfunction of the GR in BPD by measuring gene methylation status (Martin-Blanco et al., 2014; Steiger, Labonte, Groleau, Turecki, & Israel, 2013). Furthermore, studies that investigated the HPA axis function in BPD mostly revealed higher basal cortisol concentrations in concert with reduced feedback sensitivity, (Wingenfeld, Spitzer, Rullkötter, & Löwe, 2010), suggesting altered GR sensitivity. In line with the hypothesis of altered feedback sensitivity of the HPA axis in BPD, an exaggerated ACTH and cortisol response in the combined DEX/CRF test has been found, especially among those who reported childhood abuse (Rinne et al., 2002). In sum, there is evidence for altered GR functioning in BPD, while MR function seems intact. However, no study specifically addressed MR function and cognitive function in BPD.

Therefore, the aim of the current study was to further investigate the effects of MR stimulation by fludrocortisone on cognitive function in patients with BPD. We examined verbal memory, visuospatial memory, and working memory in 39 medication-free female patients with BPD and 39 age-, and education-matched healthy control women. Based on our results of enhanced social cognition after fludrocortisone in healthy controls and BPD patients (Wingenfeld et al., 2014) and our work suggesting improved cognition after fludrocortisone in healthy controls (Hinkelmann et al., 2015), we hypothesized that, across groups, fludrocortisone would improve memory function.

## 2. Experimental procedures

### 2.1. Participants

Patients with BPD were recruited from a specialized personality disorder clinic at the Department of Psychiatry and Psychotherapy, Charité University Medical School, Berlin. As most of BPD patients in clinical samples are female (Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004), we restricted the sample to women. All participants were free of psychotropic medication. Participants were excluded if they had any of the following medical conditions: CNS diseases or severe somatic diseases, metabolic or endocrine diseases, autoimmune diseases, current infections, or pregnancy. Further exclusion criteria were schizophrenia, schizoaffective disorder, bipolar disorder, depressive disorder with psychotic features, anorexia, alcohol or drug dependence (all assessed by MINI-International Neuropsychiatric Interview) (Sheehan et al., 1998). All patients had negative urine drug screening (benzodiazepines, opiates, cocaine, amphetamines, and cannabinoids) at hospital admission. Healthy participants were recruited by public postings and received financial remuneration (80€). All participants underwent a screening procedure consisting of a medical and psychiatric history questionnaire (evaluating current and lifetime psychiatric diagnosis and medical history, use of medication, alcohol, substance abuse, and smoking), and a routine medical examination. Healthy subjects were free of former and present DSM-IV axis I

or axis II disorders according to the MINI and Structured Clinical Interview for DSM-IV axis II (First, Gibbon, Spitzer, Williams, & Benjamin, 1997; Sheehan et al., 1998), had no physical illness, and had been free of any medication.

The study was approved by the local ethics committee. After complete description of the study to the subjects, written informed consent was obtained.

### 2.2. Procedure

A placebo-controlled, within-subject, cross-over study with three days in between test days was performed. Participants received either 0.4 mg fludrocortisone (Astonin® H, MerckSerono) orally or placebo. The order of administration (fludrocortisone vs. placebo) was randomized. All subjects were tested in the afternoon between 14:00 h and 17:00 h with medication being administered at 14:00 h. Fludrocortisone reaches plasma concentration peaks after 1.7 h after oral drug intake (see database DRUGDEX, 2009, half-life more than 3.5 h), and, thus, after a 90-min break following oral drug administration, participants underwent cognitive testing when the maximum effect of fludrocortisone is expected. As shown by our previous work, fludrocortisone lowers cortisol level due to the inhibitory effects of MR stimulation on HPA axis (Otte et al., 2003, 2015). In the afternoon endogenous cortisol levels are low and, thus, MR are less occupied. Therefore, we choose the afternoon for testing to reach the maximum effect of exogenous MR stimulation.

To measure potential effects of the medication on blood pressure, systolic and diastolic blood pressure was assessed prior to medication intake, 120 min after drug intake and after testing (180 min after drug intake) by an automatic device (Carescape V100, GE Healthcare).

The time course is shown in Table 1.

### 2.3. Memory tasks

To measure visuospatial memory the *Rey–Osterrieth complex figure test (RCFT)* and *Taylor complex figure test (TCFT)* (Osterrieth, 1944) were performed. 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.

Furthermore, the *Auditory Verbal Learning Test (AVLT)* (Lezak, 1995) was used to test declarative memory performance. The AVLT is a measure of short-term and long-term verbal memory. The experimenter reads a list of 15 words (list A), which the participant is requested to repeat in loose order. There are five such learning trials. After 30 min, the subject is again asked to repeat the words from list A (delayed recall).

To test working memory *digit span forward and backward* was used (Tewes, 1991). This task forms part of the Wechsler Adult Intelligence Scale (WAIS). During the forward digit span task, participants are asked to remember a series of digits and repeat them back in the same order. During the backward digit span task, they are asked to repeat the digits in reverse order.

### 2.4. Statistical analysis

Statistical analyses were performed using SPSS Version 18.0. Demographic data were analyzed using Pearson's Chi<sup>2</sup>-test for categorical data and Student's *t*-test for continuous data. Effects of fludrocortisone on cognition were analyzed using repeated measures analysis of variance (ANOVA) with the main factors condition (fludrocortisone vs. placebo) and group (BPD vs. controls). As groups differed in BMI, smoking and use of oral contraceptives, we tested whether these variables had an influence on the used memory task (ANCOVA).

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