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Enhanced Emotional Empathy after Mineralocorticoid Receptor Stimulation in Women with Borderline Personality Disorder and Healthy Women

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The mineralocorticoid receptor (MR) is highly expressed in the hippocampus and prefrontal cortex. MR have an important role in appraisal processes and in modulating stress-associated emotional reactions but it is not known whether the MR affects empathy. Borderline personality disorder (BPD) is characterized by disturbed emotion regulation and alterations in empathy. In the current study, we examined whether stimulation of the MR enhances empathy in patients with BPD and healthy individuals. In a placebo-controlled study, we randomized 38 women with BPD and without psychotropic medication, and 35 healthy women to either placebo or 0.4 mg fludrocortisone, an MR agonist. Subsequently, all participants underwent two tests of social cognition, the Multifaceted Empathy Test (MET) and the Movie for the Assessment of Social Cognition (MASC), measuring cognitive and emotional facets of empathy. Eighteen BPD patients and 18 healthy women received placebo, whereas 20 BPD patients and 17 healthy women received fludrocortisone. In the MET, fludrocortisone enhanced emotional empathy across groups, whereas cognitive empathy was not affected. In the MASC, no effect of fludrocortisone could be revealed. In both tests, BPD patients and healthy women did not differ significantly in cognitive and emotional empathy and in their response to fludrocortisone. Stimulation of MR enhanced emotional empathy in healthy women and in BPD patients. Whether fludrocortisone might have a therapeutic role in psychotherapeutic processes, remains to be elucidated.
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INTRODUCTION

Stress leads to an increase in glucocorticoid secretion, ie, cortisol in humans and cortisone in rodents, which influence a wide range of cognitive and emotional functions such as memory performance, fear-motivated behavior, or stress-associated emotional reactions (de Kloet, 2013). Glucocorticoids mediate their effects by binding to two receptors, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR), which differ in their affinity and distribution within the brain (Lupien and Lepage, 2001; de Kloet *et al*, 2005; Joels *et al*, 2008; Roozendaal *et al*, 2010). Although most of the effects of GCs have been attributed to GR, more recent studies emphasize the importance of MR (Joels *et al*, 2008; de Kloet, 2010; Harris *et al*, 2012). Indeed, it has been consistently shown that blocking the MR leads to impaired cognitive function in humans (Otte *et al*, 2007; Cornelisse *et al*, 2011; Rimmele *et al*, 2013). Interestingly, these impairing effects of MR blockade were most pronounced for emotional memory (Rimmele *et al*, 2013). This fits very well with animal data showing that MR are particularly involved in the appraisal of novel situations and in modulating stress-associated emotional reactions (Ter Horst *et al*, 2012; de Kloet, 2013; Kruk *et al*, 2013).

As humans often have to perform complex social cognitive tasks while being stressed, it is of great interest to understand how stress and stress hormones influence social cognition, ie, the ability to process, store, and use information about other people and social situations. A phenomenon closely related to social cognition is empathy, which consists of at least two components: the first is a cognitive component that captures the capacity to infer others' mental states and is also referred to as perspective taking, mentalizing, or theory of mind (Zaki and Ochsner, 2012). Second, empathy also comprises an affective component, ie, an emotional response to another person's emotional state (Blair, 2008; Roepke *et al*, 2012). One task to investigate both components of empathy is the 'Multifaceted Empathy Test' (MET) (Dziobek *et al*, 2008). Another task that was developed to assess cognitive empathy in a more ecologically valid fashion, is the 'Movie for the

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Assessment of Social Cognition' (MASC) (Dziobek *et al*, 2006), which is a video-based task demanding test takers to infer emotions, thoughts, and intentions of characters engaged in social interactions. An elegant study used the MASC to investigate the association between the cortisol response to a psychosocial stressor and cognitive empathy (Smeets *et al*, 2009). In women, elevated cognitive empathy was found for those who responded with low cortisol to stress exposure. Furthermore, in women, there was a negative association between cortisol reactivity and MASC scores (Smeets *et al*, 2009). In men, an opposite pattern was seen, with high cortisol responders showing greater MASC scores and a negative correlation between stress hormones and empathy. Thus, this study suggests sex-specific effects of glucocorticoids on social cognition.

Deficits in social cognition are discussed for several mental disorders, including borderline personality disorder (BPD) (Roepke *et al*, 2012). Of note, many of the symptoms seen in BPD occur within social contexts, leading to the assumption that BPD might be characterized by aberrant social cognition. Indeed, impairments were seen in previous studies using the MET to assess cognitive and emotional empathy (Preissler *et al*, 2010; Dziobek *et al*, 2011). In the emotional empathy items of the MET, participants were required to rate the amount of mirroring of an emotion that took place in response to a picture (eg, if the mental state of the person was anxious, subjects were asked to rate how anxious they felt) and additionally rated the degree of empathic concern they felt for the person in the picture. Results from the MET revealed that BPD patients had significantly reduced tendencies to feel empathy for other people in emotionally distressing situations compared with non-clinical controls (Dziobek *et al*, 2011).

On the basis of the findings of a negative association between cortisol reactivity and cognitive empathy in women (Smeets *et al*, 2009) and the impairing effects of selective MR blockade on emotional memory and cognitive performance (Otte *et al*, 2007; Cornelisse *et al*, 2011; Rimmele *et al*, 2013), we hypothesized that selective MR stimulation with fludrocortisone would enhance cognitive and emotional empathy in healthy women. Furthermore, we included a clinical group of patients with BPD for which deficits in cognitive and emotional empathy have been demonstrated (Dziobek *et al*, 2011). We hypothesized that fludrocortisone would improve cognitive and emotional empathy in BPD.

MATERIALS AND METHODS

Participants

In total, 38 women with BPD and 35 healthy women were recruited and completed the study. 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 abuse, and dependence in the last 6 months (all assessed by MINI-International Neuropsychiatric Interview). All patients had negative urine drug screening (benzodiazepines, opiates, cocaine, amphetamines, and cannabinoids) during hospital admission. Written informed consent was obtained from all participants. Healthy participants were recruited by local advertisement and received financial remuneration (80€). The study was approved by the Medical Councils' Ethics Committee of Hamburg and Berlin.

Procedure

We used the MINI to assess current psychiatric diagnoses (Sheehan *et al*, 1998, German version Ackenheil *et al*, 1999). BPD was diagnosed using the Structured Clinical Interview for DSM-IV axis II (First *et al*, 1997). Clinical interviews were conducted by two trained PhD psychologists (KJ and LK).

A placebo-controlled study was performed and participants were randomized (simple randomization) to either 0.4 mg fludrocortisone (Astonin H, MerckSerono) orally or to placebo. Drugs were administered at 14:00 h and testing took place between 15:45 and 16:45 h. Fludrocortisone exhibits its maximum effects after 1.7 h after drug intake (DRUGDEX). We did not use a within-subject design because no parallel versions of the MET and MASC were available. The participants were tested in a quiet room and were allowed to drink some water.

Social Cognition Tasks

MET. To assess cognitive and emotional empathy, the MET was used (Dziobek *et al*, 2008) in a modified version (Hurlemann *et al*, 2007; Dziobek *et al*, 2011; Ritter *et al*, 2011). The MET is a PC-assisted test consisting of photographs that show 30 picture stimuli with people in emotionally charged situations. To assess cognitive empathy, participants were required to infer the mental state of the subject in the photo and were asked to indicate the correct one from a list of four. To assess emotional empathy, participants were asked to rate the degree of empathic concern they felt for the person in the picture (Likert scale, 0 = not at all, 9 = very much). Pictures were presented in six blocks of 10 picture stimuli. In the first block, participants were asked for cognitive empathy. In the next blocks, it was asked for emotional and cognitive empathy in alternating order. In this way, each picture was rated for cognitive and emotional empathy. The score range is 0–30 for the cognitive empathy and 30–270 for the emotional empathy.

MASC. In addition, we administered the MASC, a sensitive video-based test for the evaluation of cognitive empathy (Dziobek *et al*, 2006; Preissler *et al*, 2010; Ritter *et al*, 2011). This task involves watching a 15 min movie about four characters spending an evening together and answering questions referring to the actors' mental states. The movie stops 45 times, when questions about the actors' feelings/emotions (score range 0–15), thoughts (score range 0–4), and intentions (score range 0–14) are asked. Participants are required to choose the correct answer out of four possible ones.

Statistical Analysis

Statistical analyses were performed using SPSS Version 18.0. Demographic data were analyzed using Pearson's χ^2-test for categorical data and Student's *t*-test for continuous data. Effects of fludrocortisone on social cognition were analyzed using analysis of variance (ANOVA) with the main factors treatment (fludrocortisone *vs* placebo) and group (BPD *vs* controls). In a second step, all analyses were controlled for BMI, years of school education (covariate), smoking, and intake of oral contraceptives (additional factor).

RESULTS

Demographic and Clinical Data

In BPD patients, the following current comorbid axis I disorders were reported: major depressive disorder $n=9$, dysthymia $n=5$, panic disorder $n=2$, agoraphobia $n=5$, social phobia $n=7$, obsessive compulsive disorder $n=2$, PTSD $n=5$, bulimia nervosa $n=2$, substance abuse $n=5$, and alcohol abuse $n=2$. None of the patients fulfilled the criteria of antisocial personality disorder.

BPD patients and healthy women did not differ with regard to age. Healthy women had slightly more years of education and had a slightly lower body mass index. There were more smokers in the patient group, whereas more healthy women took oral contraceptives (sample characteristics are presented in Table 1). All variables that differed significantly between patients and healthy women were controlled for in statistical analyses.

Effects of Fludrocortisone *vs* Placebo on Cognitive and Emotional Empathy

In our placebo-controlled study, 18 BPD patients and 18 healthy women received placebo, whereas 20 BPD patients and 17 healthy women received fludrocortisone. There were missing data for two BPD patients in the MASC.

MET

First, we performed an ANOVA with repeated measurements analyzing the effect of fludrocortisone (between-subject factor 'treatment') on emotional and cognitive empathy (within-subject factor 'test score') in patients with BPD and healthy control (between-subject factor 'group'). A main effect treatment ($p=0.008$) as well as a test score by treatment-interaction effect ($p=0.01$) could be revealed, whereas there was no main effect group ($p=0.13$) or treatment by group interaction effect ($p=0.56$). This result suggests a differential effect on fludrocortisone on emotional and cognitive empathy.

To clarify this test score by treatment-interaction effect, separate ANOVAs were conducted to further analyze the effects of fludrocortisone on cognitive and emotional empathy with group (BPD *vs* controls) and treatment (fludrocortisone *vs* placebo) as between-subject factors.

Emotional empathy was enhanced in the fludrocortisone condition compared with placebo across groups (main effect treatment $F_{df1,69}=7{,}1$, $p=0.009$). There was no significant group ($F_{df1,69}=2{,}1$, $p=0.15$) or treatment by group interaction ($F_{df1,69}=0{,}4$, $p=0.55$) effect, suggesting a similar effect of fludrocortisone on emotional empathy across groups (see Figure 1) and no differences between BPD patients and healthy women in emotional empathy across treatment modalities (BPD mean: 148 (49) range 30–239; controls mean: 161 (42) range 61–266). The results did not change in the ANCOVA controlling for the above-mentioned confounders, ie, body mass index, smoking, and education. The improving effect of fludrocortisone on emotional empathy was seen for positive ($p=0.016$) as well as for negative ($p=0.041$) emotions. The effect size (Cohen's *d*) of the effect of fludrocortisone on emotional empathy was $d=0.63$ across groups, indicating a medium effect (BPD patients $d=0.73$, healthy controls $d=0.53$).

In the cognitive part of the MET, there was no effect of the main factor treatment and no significant group effect or treatment by group interaction (all *p*-values >0.55) could be revealed. Thus, there was no difference between BPD patients and healthy women in cognitive empathy across treatment modalities (BPD mean (SD): 19.5 (2.9) range 14–26; controls mean: 20.3 (3.1) range 14–27). Controlling for potentially confounding variables using ANCOVA did not change these results.

MASC

Separate ANOVAs were conducted to analyze the effects of fludrocortisone on cognitive empathy, ie, the inferring of emotions, thoughts, and intentions in the MASC with group (BPD *vs* controls) and treatment (fludrocortisone *vs* placebo) as between-subject factors. Mean values and SD are presented in Table 2.

Concerning the subscore 'emotions', we found a significant effect of the main factor group in unadjusted analyses ($F_{df1,67}=4{,}31$, $p=0.04$) but this effect did not hold after controlling for potential confounders ($p=0.68$). There was no main effect of treatment or group by treatment-interaction effect (both *p*-values >0.28).

Table 1 Sample Characteristics

	BPD	Healthy women	Statistics
Age (mean (SD))	24.3 (5.7)	25.5 (5.6)	$t_{df71}=-0.86$, $p=0.40$
Years of school education (mean (SD))	10.2 (1.5)	11.0 (1.5)	$t_{df67}=-2.31$, $p=0.02$
Body mass index (mean (SD))	26.0 (7.1)	23.6 (5.0)	$t_{df71}=-1.65$, $p=0.10$
Smoker (yes/no)	27/11	10/24	$\chi^2=12.45$, $p<0.001$
Intake of oral contraceptives (yes/no)	9/29	16/19	$\chi^2=4.76$, $p=0.03$

Abbreviation: BPD, borderline personality disorder.

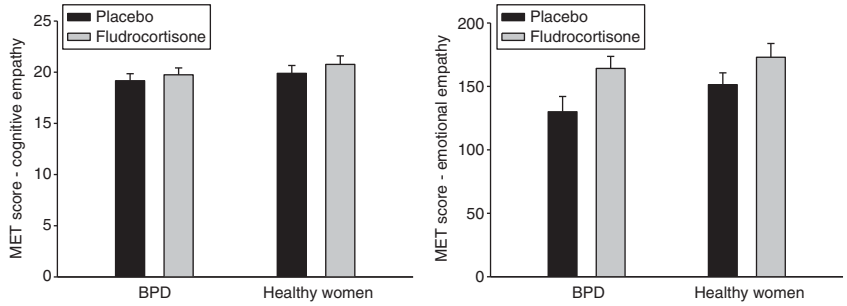

Figure 1 Cognitive and emotional empathy measured with the Multifaceted Empathy Test (MET) after fludrocortisone administration and placebo in patients with BPD and healthy women. A significant main effect of treatment was found for the emotional test part ($p = 0.009$).

Table 2 Cognitive Empathy Measured with the MASC after Fludrocortisone Administration and Placebo in Patients with BPD and Healthy Women

MASC (mean/SD)	BPD	Healthy women
Placebo	$n = 17$	$n = 18$
Recognition of emotions	11.41 (2.2)	12.06 (1.4)
Recognition of thoughts	3.29 (0.7)	3.28 (0.8)
Recognition of intentions	10.94 (2.1)	10.33 (0.9)
Fludrocortisone	$n = 19$	$n = 17$
Recognition of emotions	10.53 (2.0)	11.88 (2.4)
Recognition of thoughts	3.16 (1.0)	3.12 (1.0)
Recognition of intentions	9.79 (1.9)	10.59 (2.7)

Abbreviations: BPD, borderline personality disorder; MASC, Movie for the Assessment of Social Cognition.

No significant main effect of group, treatment, or group by treatment-interaction effect (all p-values >0.49) could be revealed for the subscore 'thought'. Similarly, there was no significant main effect of group, treatment, or group by treatment-interaction effect (all p-values >0.15) for the subscore 'intentions'. These results did not change after controlling for potentially confounding variables.

DISCUSSION

This study examined the effects of MR stimulation via fludrocortisone administration on cognitive and emotional empathy in women with BPD and in healthy women. In line with our hypothesis, MR stimulation led to enhanced emotional empathy, whereas, contrary to our hypothesis, cognitive empathy was not clearly influenced by fludrocortisone. Remarkably, we found enhanced emotional empathy after fludrocortisone across groups, in healthy women as well as in women with BPD. Patients and healthy participants did not differ significantly in cognitive and emotional empathy across treatment modalities.

This is the first study to examine the effects of MR stimulation on social cognition in humans. Our result that fludrocortisone enhances emotional empathy fits very well with animal data. MR are particularly involved in the appraisal of novel situations and in selection of response strategies (de Kloet, 2013). In this context, MR are important in modulating stress-associated emotional arousal and adaptive behaviors (Brinks *et al*, 2007). Of note, in a stressful situation, the individual needs to decide immediately how to act and emotional appraisal and reaction is often essential for fast reaction in the context of perceived danger and anxiety. MR are expressed in high density in limbic brain areas, which are involved in the processing of emotional information (Joels *et al*, 2011; Groeneweg *et al*, 2012). Indeed, blockade of MR impaired memory performance particularly for emotional material (Rimmele *et al*, 2013). Therefore, it is plausible that MR influences emotional empathy given that emotional empathy, ie, the ability to share the emotional experience of another person, contributes importantly to appraisal processes and emotional reactions especially in stressful situations. Obviously, the degree of emotional empathy that a person is feeling (or not feeling) in a given situation modulates the appraisal of that situation and response strategies (Ter Horst *et al*, 2012; de Kloet, 2013; Kruk *et al*, 2013). However, at present, it remains unclear why MR stimulation improves emotional but not cognitive empathy and further studies need to replicate and further explore these findings (Zhou *et al*, 2011).

Our study has potentially important clinical implications. Intranasal oxytocin, a peptide that exerted positive effects on empathy (Meyer-Lindenberg *et al*, 2011), has already been used in pilot studies to examine whether there are synergistic effects of oxytocin and psychotherapy in depressed patients (Macdonald *et al*, 2013). Similarly, stimulation of MR could be potentially used to enhance emotional empathy and thus, therapeutic alliance and learning effects in psychotherapeutic settings. Preclinical animal data are consistent with this idea, because female mice with forebrain-specific deletion of the MR gene were unable to show extinction of contextual fear, and could not discriminate between cue and context fear unlike control mice (Ter Horst *et al*, 2012). In contrast, forebrain MR overexpression enhanced memory and reduced anxiety (Lai *et al*, 2007; Rozeboom *et al*, 2007). Therefore, a combination of MR stimulation with psychotherapeutic interventions might provide new avenues for a better treatment of BPD that is characterized by disturbed emotion regulation and emotional social interaction pathology.

We did not find significant differences between BPD patients and healthy women with regard to cognitive and

emotional empathy across treatment modalities in our study as suggested by some, but not all, previous studies (Dziobek *et al*, 2011; Schilling *et al*, 2012). Of note, some authors even discussed increased cognitive and emotional empathy in BPD (Roepke *et al*, 2012; Dinsdale and Crespi, 2013). In our study we found, on a descriptive level, diminished emotional empathy in BPD with an effect size of Cohen's $d = 0.2$ in the placebo condition, which corresponds to a small effect. It might be also the case that the used tasks that have been developed for autism spectrum disorders are not specific enough to detect BPD specific alterations in empathy, as also suggested for other tasks in the context of social cognition, eg, the 'Reading the Mind in the Eyes Test' (Schilling *et al*, 2012). Of note, using the MASC, has been shown that comorbid PTSD strongly influences cognitive empathy in a sample of BPD patients (Preissler *et al*, 2010). Thus, the relatively low prevalence of PTSD in the current study might be one reason for the unimpaired performance of the BPD patients in cognitive empathy. Furthermore, cognitive and emotional empathy in a given situation might depend on the level of arousal in that situation with decreasing empathy capacities in the face of increasing arousal (Dziobek *et al*, 2011; Ripoll *et al*, 2013). In our study, no stress paradigm was used and future studies should further examine the association between arousal and empathy in BPD.

There are some limitations of the study to be mentioned. First, the sample was too small to perform subgroup analyses, eg, with regard to comorbid mental disorders as major depressive disorder or PTSD. These disorders are known to influence cognitive empathy and HPA axis (Wingenfeld *et al*, 2010; Roepke *et al*, 2012; Wingenfeld *et al*, 2013). Furthermore, only women were included in this study and, therefore, no conclusions can be drawn with regard to men. Of note, first animal data indicate that MR mediates differences in emotional and cognitive behaviors between female and male mice (Ter Horst *et al*, 2012). Thus, our results need replication in a larger sample addressing comorbidities and potential sex effects. Menstrual cycle phase was not controlled for. However, intake of oral contraceptive did not influence the results. Furthermore, we did not ask the participant about side effects or if they had any hypotheses whether they received active treatment or not. Finally, although fludrocortisone has an about 15-fold higher affinity to MR compared with GR (Agarwal *et al*, 1977), we cannot completely rule out some GR effects of fludrocortisone. Dose-response studies are needed in this regard to disentangle MR from GR effects. Furthermore, we did not include a measure of current mood states during the examination. Thus, we cannot rule out that our results are secondary to an overall induced emotionality. In addition, further studies should include other measures of empathy and compare BPD patients and healthy participants with high emotional empathy scores with those with lower emotional empathy with respect to their response to MR stimulation. Future studies should examine whether fludrocortisone affects mood state and arousal of the participants and whether this is related to the degree of empathy.

In summary, this is the first study demonstrating enhanced emotional empathy after MR stimulation in BPD patients and healthy women. Clearly, further research on MR function and potential therapeutic effects of MR stimulation on emotional and cognitive processes in stress-related disorders such as BPD is warranted.

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The authors declare no conflict of interest.

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