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DISSERTATION

Aspects of Social Cognition and Memory in Patients with Borderline Personality Disorder

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1. SUMMARY

1.1 ABSTRACT (GERMAN)

Die Borderline Persönlichkeitsstörung (BPS) und die Posttraumatische Belastungsstörung (PTBS) sind hochkomorbide Störungen, die sowohl durch Störungen der Emotionalität als auch durch interpersonelle Auffälligkeiten gekennzeichnet sind. In der Literatur werden diese Aspekte häufig unter dem Konzept der sozialen Kognition subsumiert. Studien, die Aspekte sozialer Kognition bei Patienten mit BPS untersucht haben, belegen Abweichungen, beispielsweise bezüglich Empathievermögen im Vergleich zu gesunden Kontrollen (Roepke, Vater, Preissler, Heekeren, & Dziobek, 2012). Bezüglich des Konzepts der emotionalen Intelligenz ist die Studienlage inkonsistent (Beblo et al., 2010; Peter, Arntz, Klimstra, & Vingerhoets, 2018).

Beeinträchtigungen der sozialen Kognition sind bei Patienten mit PTBS ebenfalls gut untersucht (Stevens & Jovanovic, 2019), valide Daten zu emotionaler Intelligenz bei PTBS gibt es nach aktuellem Forschungsstand hingegen nicht.

Wir haben daher emotionale Intelligenz bei 53 Patienten mit BPS ohne PTBS, 30 Patienten mit PTBS mit BPS, 41 Patienten mit PTBS ohne BPS und bei 63 gesunden Kontrollprobanden mit dem Test of Emotional Intelligence (TEMINT) untersucht. Patienten mit BPS unterschieden sich nicht signifikant von den gesunden Kontrollprobanden. Nur Patienten mit PTBS ohne BPS zeigten Beeinträchtigungen in der emotionalen Intelligenz verglichen mit Patienten mit BPS ohne PTBS und gesunden Kontrollprobanden. Diese Beeinträchtigungen waren nicht auf bestimmte Emotionen beschränkt.

Patienten mit BPS erleben hohe Anspannungszustände. Diese haben einen Einfluss auf die soziale Kognition (Sharp et al., 2011). Hohe Anspannungszustände, in anderen Worten Stress, führen zur Ausschüttung von Glukokortikoiden. Diese beeinflussen kognitive und emotionale Funktionen, indem sie an zwei Typen von Rezeptoren im Gehirn binden: Mineralokortikoidrezepotoren (MR) und Glukokortikoidrezeptoren (GR) (Vogel, Fernandez, Joels, & Schwabe, 2016). Insbesondere die Einflüsse von MR Aktivierung auf emotionale und kognitive Prozesse der BPS sind relevant, um Abweichung der (sozialen) Kognition der BPS zu verstehen. In einer randomisierten placebokontrollierten Studie haben wir den Einfluss der Stimulation des MR mit Fludrocortison auf Empathie und Gedächtnis bei Frauen mit BPS und gesunden Kontrollprobandinnen untersucht. Gedächtnis wurde mit dem Rey–Osterrieth Complex

Figure Test (RCFT) und dem Taylor Complex Figure Test (TCFT), dem Auditory Verbal Learning Test (AVLT), und dem Digit Span Forward and Backward untersucht. Empathie wurde mit dem Multifaceted Empathy Test (MET) und dem Movie for the Assessment of Social Cognition (MASC) untersucht. Frauen mit BPS unterschieden sich nicht signifikant in emotionaler oder kognitiver Empathie von Gesunden. Stimulation des MR verbesserte die emotionale Empathiefähigkeit bei Gesunden und bei Frauen mit BPS. Außerdem zeigten sich bei Frauen mit BPS Beeinträchtigungen im verbalen und räumlichen Gedächtnis sowie Verbesserungen im Arbeitsgedächtnis in beiden Gruppen.

1.2 ABSTRACT (ENGLISH)

Borderline personality disorder (BPD) and Posttraumatic stress disorder (PTSD) are highly comorbid disorders and are characterized by aspects of social and emotional dysfunctioning. One concept that captures these features is social cognition. Studies about aspects of social cognition in patients with BPD propose aberrant social cognition e.g., alterations in empathy compared to healthy controls (Roepke et al., 2012) and displayed inconsistent results regarding emotional intelligence (Beblo et al., 2010; Peter et al., 2018). Patients with PTSD show impairments in social cognition (Stevens & Jovanovic, 2019) as well, whereas emotional intelligence in PTSD has not been investigated so far.

We assessed emotional intelligence via the Test of Emotional Intelligence (TEMINT) in patients with BPD without comorbid PTSD (n = 53), in patients with PTSD with comorbid BPD (n = 30), and in patients with PTSD without comorbid BPD (n = 41), as well as in 63 healthy controls. Patients with BPD did not differ significantly from healthy controls. Only patients with PTSD without comorbid BPD showed impairments in emotional intelligence compared to patients with BPD without PTSD, and compared to healthy controls. These impairments were not restricted to specific emotions.

Patients with BPD experience high levels of arousal that influence social cognition (Sharp et al., 2011). Arousal, in other words, stress, leads to an increase in glucocorticoid secretion, which influences cognitive and emotional functions by activating two types of receptors in the brain: mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) (Vogel et al., 2016). Especially the effects of MR occupation on emotion and cognitive function in BPD are relevant to understand alterations in social cognition and in cognition. In two randomized placebo-controlled studies, we examined the influence of stimulation of the MR via fludrocortisone administration on empathy and memory in women with BPD and healthy controls. Memory was investigated with the Rey–Osterrieth Complex Figure Test (RCFT) and the Taylor Complex Figure Test (TCFT), the Auditory Verbal Learning Test (AVLT), and the Digit Span Forward and Backward Task. Empathy was measured by the Multifaceted Empathy Test (MET) and the Movie for the Assessment of Social Cognition (MASC). We found that patients with BPD did not differ from healthy controls in emotional or cognitive empathy. Stimulation of MR enhanced emotional empathy in healthy women

and in patients with BPD. Furthermore, we found impaired verbal and visuospatial memory performance in BPD, but improved working memory in both groups.

1.3 INTRODUCTION

Borderline Personality Disorder (BPD) is characterized by a pervasive pattern of instability of interpersonal relationships, self-image, affects, and marked impulsivity that begins in early childhood and is present in a variety of contexts (American Psychiatric Association, 2013). It affects approximately 2.7% of the general population (Trull, Jahng, Tomko, Wood, & Sher, 2010) and is known to be a severe disorder associated with many comorbidities and psychosocial impairments (Skodol et al., 2002). One very frequent comorbidity of BPD is Posttraumatic Stress Disorder (PTSD). PTSD is present in up to 56% of patients with BPD (Zanarini et al., 1998) and is therefore chosen as a clinical control group. PTSD is a severe psychiatric disorder too, marked by intrusion symptoms, persistent avoidance of stimuli, negative alterations in cognition and mood as well as in arousal reactivity, all associated with the occurred traumatic event (American Psychiatric Association, 2013). It affects up to 3.5% of the general population in the USA (Kessler, Chiu, Demler, & Walters, 2005) and 1.1-2.9% of the population in Europe (Wittchen et al., 2011). We already know that BPD and PTSD share common characteristics like high prevalence rates of experienced traumatic events and poor quality of interpersonal relationships (Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004; Nietlisbach, Maercker, Rossler, & Haker, 2010). Still, we do not know where these interpersonal disturbances derive from. One model that captures different aspects of social interaction, and has therefore often been the scope of research, is social cognition. Social cognition is an umbrella term for various constructs as empathy, emotional intelligence, and theory of mind. Empathy consists of two distinguishable components. One is an affective component, meaning one's emotional response to another person`s affective state, called emotional empathy. The other one is a cognitive component, which means the ability to represent the mental states of others, often referred to as cognitive empathy, mentalizing, or theory of mind (Blair, 2005; Roepke et al., 2012). Emotional intelligence as another aspect of social cognition has been defined as the "ability to carry out accurate reasoning focused on emotions and the ability to use emotions and emotional knowledge to enhance thought." (Mayer, Roberts, & Barsade, 2008). Many researchers have focused on social cognition in BPD and conducted studies with partially conflicting results (see e.g. Dinsdale & Crespi, 2013; Roepke et al., 2012 for review). Cognitive empathy seems to be impaired when focusing on theory of mind (Nemeth et al., 2018), or facial emotion recognition abilities and mentalizing

(Anupama, Bhola, Thirthalli, & Mehta, 2018). There is evidence that cognitive empathy is negatively influenced by the complexity and ecological validity of the task (Roepke et al., 2012; Sosic-Vasic et al., 2019), by high arousal, or emotional states (Sharp et al., 2011) as well as by anamnesis of trauma or comorbid PTSD (Duque-Alarcon, Alcala-Lozano, Gonzalez-Olvera, Garza-Villarreal, & Pellicer, 2019; Preissler, Dziobek, Ritter, Heekeren, & Roepke, 2010). Regarding emotional empathy in BPD, there are researchers proposing altered (Niedtfeld, 2017) or impaired emotional empathy (Roepke et al., 2012), especially in emotionally distressing situations (Dziobek et al., 2011), whereas others did not find impairments (Jeung & Herpertz, 2014 for review). Findings regarding impairments in emotional intelligence in BPD are also inconsistent (Beblo et al., 2010; Hertel, Schutz, & Lammers, 2009; Hurtado, Trivino, Arnedo, Roldan, & Tudela, 2016; Peter et al., 2018; Peter et al., 2013). All in all, social cognition in BPD seems to be aberrant compared to healthy controls (Roepke et al., 2012).

Patients with PTSD have demonstrated deficits in social cognition (Mazza et al., 2012; Sharp, Fonagy, & Allen, 2012; see Stevens & Jovanovic, 2019 for review). Trauma load has been associated with lower social cognitive performance (Barzilay et al., 2019) and PTSD symptom severity has been associated with reduced emotional and cognitive empathy (Palgi, Klein, & Shamay-Tsoory, 2017). Evidence for altered brain activity in specific regions activated by empathy in PTSD patients has also been found (Mazza et al., 2012). Contrary to this, one study found lower empathic resonance and higher personal distress but no clear indication of other impaired social cognitive functions (Nietlisbach et al., 2010). Many studies analyzed predispositional factors for developing PTSD and identified interpersonal factors like social support, quality of intimate relationships and social cognition as key factors for trauma processing and recovery (McGuire et al., 2018; Nietlisbach et al., 2010; Sharp et al., 2012). To our knowledge, emotional intelligence has not been investigated in patients with PTSD, although aspects of emotional dysfunction such as emotional numbing and disturbed relatedness are characteristic features of PTSD.

According to this database, we investigated emotional intelligence in patients with BPD without PTSD, PTSD with comorbid BPD, PTSD without BPD, and healthy controls. We hypothesized that patients with BPD without PTSD do not show impairments in emotional intelligence compared to healthy controls. Patients with PTSD and comorbid BPD and patients with PTSD only on the other hand should display impairments in emotional intelligence compared to healthy controls. These impairments should concern

especially PTSD-associated emotions like “anger”, “fear”, “sadness” and “guilt” (American Psychiatric Association, 2013) compared to patients with BPD without PTSD and to healthy controls.

Patients with BPD are well known for experiencing high levels of arousal, in other words stress. Stress has an important impact on memory and social cognition in healthy humans (Vogel et al., 2016). There is also evidence that arousal has an influence on social cognition in BPD (Sharp et al., 2011). Therefore, one possible explanation for alterations in cognition and social cognition in BPD are dysregulations of the hypothalamic-pituitary-adrenal (HPA) axis (Bourvis, Aouidad, Cabelguen, Cohen, & Xavier, 2017). In fact, BPD can be and has been conceptualized as a neuroendocrinological disease (Ferreira, Alves, Oliveira, & Avelino, 2017). Studies that investigated the HPA-axis in BPD found enhanced cortisol release and HPA axis hyperactivity together with reduced HPA axis feedback sensitivity (see Cattane, Rossi, Lanfredi, & Cattaneo, 2017 for review; Wingenfeld, Spitzer, Rullkotter, & Lowe, 2010). Neurobiologically, stress leads to an increase of glucocorticoid secretion which influences cognitive and emotional functions by activating two types of receptors in the brain, mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) (Vogel et al., 2016; Wingenfeld et al., 2014). GR are expressed in stress responsive brain structures such as the hypothalamus, hippocampus, amygdala, and ascending aminergic neurons. MR are expressed in limbic brain structures, e.g., the hippocampus, amygdala, and prefrontal cortex (de Kloet, 2013). While the role of GR in cognitive function has been studied thoroughly, the role of MR is still under investigation. Studies have shown that blocking MR leads to impaired cognitive function in healthy humans (Otte et al., 2007), especially when emotional stimuli were presented (Rimmele, Besedovsky, Lange, & Born, 2013). Stimulating MR, on the other hand, may improve cognitive function, particularly memory functions. This was demonstrated for declarative memory consolidation (Groch, Wilhelm, Lange, & Born, 2013), for visuospatial memory, short-term, and working memory in young and elderly healthy individuals (Hinkelmann et al., 2015; Piber et al., 2016) and for verbal memory and executive functions in patients with depression and in healthy controls (Otte et al., 2015).

The investigation of effects of MR stimulation on emotion and cognitive function in BPD can be very helpful to understand alterations in cognition and social cognition (Schultebraucks et al., 2016). Therefore, our further studies focused on the effects of MR stimulation with fludrocortisone on empathy and memory in women with BPD and

healthy controls. On the basis of the findings of MR blockade on emotional memory and cognitive performance (Otte et al., 2007; Rimmele et al., 2013), we hypothesized that MR stimulation with fludrocortisone would enhance empathy in women with BPD as well as in healthy women. Based on results of improved cognition after fludrocortisone administration in healthy controls (de Kloet et al., 2016; Hinkelmann et al., 2015; Piber et al., 2016), we hypothesized that, across groups, fludrocortisone would improve memory function.

1.4 METHODS

The participants included in our studies were recruited from specialized personality disorder units of different psychiatric hospitals (Department of Psychiatry and Psychotherapy, Charité Universitätsmedizin Berlin, Germany, Department of Psychosomatic Medicine and Psychotherapy, Universitätsklinikum Hamburg-Eppendorf & Schön Klinik Hamburg-Eilbek, Germany and Department of Psychiatry and Psychotherapy, Ev. Klinikum Bethel, Germany), or, in case of healthy participants, via public postings. All diagnoses were assessed according to DSM-IV criteria by the German version of either the Structured Clinical Interview for DSM-IV Axis 1 and 2 (SCID I and SCID II) (Wittchen, Zaudig, & Fydrich, 1997) or the Mini-International Neurospychiatric Interview (M.I.N.I.) (Sheehan et al., 1998). Statistical analyses were performed using SPSS Version 22.0. Demographic data were analyzed using Pearson's Chi^2-test or Pearson’s w2-test for categorical data and Student’s t-test for continuous data. Effects of the main factors were analyzed using analysis of variance (ANOVA) and, if required, repeated measures analysis of variance (rmANOVA).

1.4.1 Study 1: Emotional Intelligence in Patients with Posttraumatic Stress Disorder, Borderline Personality Disorder, and Healthy Controls

1.4.1.1 Participants

The study included 190 participants, 71 patients with PTSD (41 patients with PTSD without BPD, 30 patients with PTSD with comorbid BPD), 56 patients with BPD without PTSD and 63 healthy controls.

1.4.1.2 Material and Procedure

The assessment of emotional intelligence was realized with the Test of Emotional Intelligence (TEMINT) (Schmidt-Atzert & Buehner, 2002). The paper-and-pencil instrument consists of 12 items with descriptions of a specific situation that a target person is experiencing. Each item is to be rated by the participants in regard of the potential emotions the target person might be feeling in that situation and in regard of the intensity of the emotions the target person might be feeling. The possible emotions were “aversion”, “anger”, “fear”, “unease”, “sadness”, “guilt”, “happiness”, “pride”, “affection” and “surprise”.

1.4.2 Study 2: Enhanced Emotional Empathy after Mineralocorticoid Receptor Stimulation in Women with Borderline Personality Disorder and Healthy Women

1.4.2.1 Participants

38 women with BPD and 35 healthy women were recruited. All participants were free of psychotropic medication.

1.4.2.2 Material and Procedure

Patients with BPD and healthy women were randomized to either placebo or 0.4 mg fludrocortisone, an MR agonist. Fludrocortisone was administered at 2 p.m., and testing took place between 3.45 p.m. and 4.45 p.m. All participants underwent two tests of social cognition, the Multifaceted Empathy Test (MET) (Dziobek et al., 2008) and the Movie for the Assessment of Social Cognition (MASC) (Dziobek et al., 2006), measuring cognitive and emotional facets of empathy. The MET is a PC-assisted, ecologically valid test consisting of photographs that show photo images of people in emotionally charged situations. To test for cognitive empathy, participants have to infer the mental state of the subject in the image. To test for emotional empathy, participants have to rate their level of empathic concern for the subject in the image. The MASC is a video-based test measuring cognitive empathy. Participants watch a 15-minute movie and have to answer questions about the actors’ feelings, thoughts, and intentions.

1.4.3 Study 3: Effects of Mineralocorticoid Receptor Stimulation via Fludrocortisone on Memory Function in Women with Borderline Personality Disorder

1.4.3.1 Participants

We recruited 39 female BPD patients and 39 female control patients. All participants were free of psychotropic medication.

1.4.3.2 Material and Procedure

Our study was a placebo-controlled, within-subject, cross-over study. Participants received either 0.4 mg fludrocortisone orally or placebo. The order of administration (fludrocortisone vs. placebo) was randomized. All subjects were tested in the afternoon between 2 p.m. and 5 p.m. with the respective substance being administered at 2 p.m. Memory was investigated with the Rey–Osterrieth Complex Figure Test (RCFT), the Taylor Complex Figure Test (TCFT) (Osterrieth, 1944), the Auditory Verbal Learning Test (AVLT) (Lezak, Howieson, Loring, & Fischer, 2004) and the Digit Span Forward and Backward Task (Tewes, 1991).

The RCFT and TCFT (Osterrieth, 1944) are instruments to measure visuospatial memory. Participants have to draw a displayed complex figure and then re-draw it from memory, first, directly (direct recall), and then, 20 minutes later (delayed recall).

The AVLT (Lezak et al., 2004) measures declarative memory performance. An instructor reads a list of 15 words to the participant, who has to repeat the words in no particular order in five different learning trials and then again after 30 minutes (delayed recall).

To test working memory, the Digit Span Forward and Backward Task was used (Tewes, 1991). Participants are asked to remember a series of digits and repeat them back in the same order (forward digit span task) or in reverse order (backward digit span task).

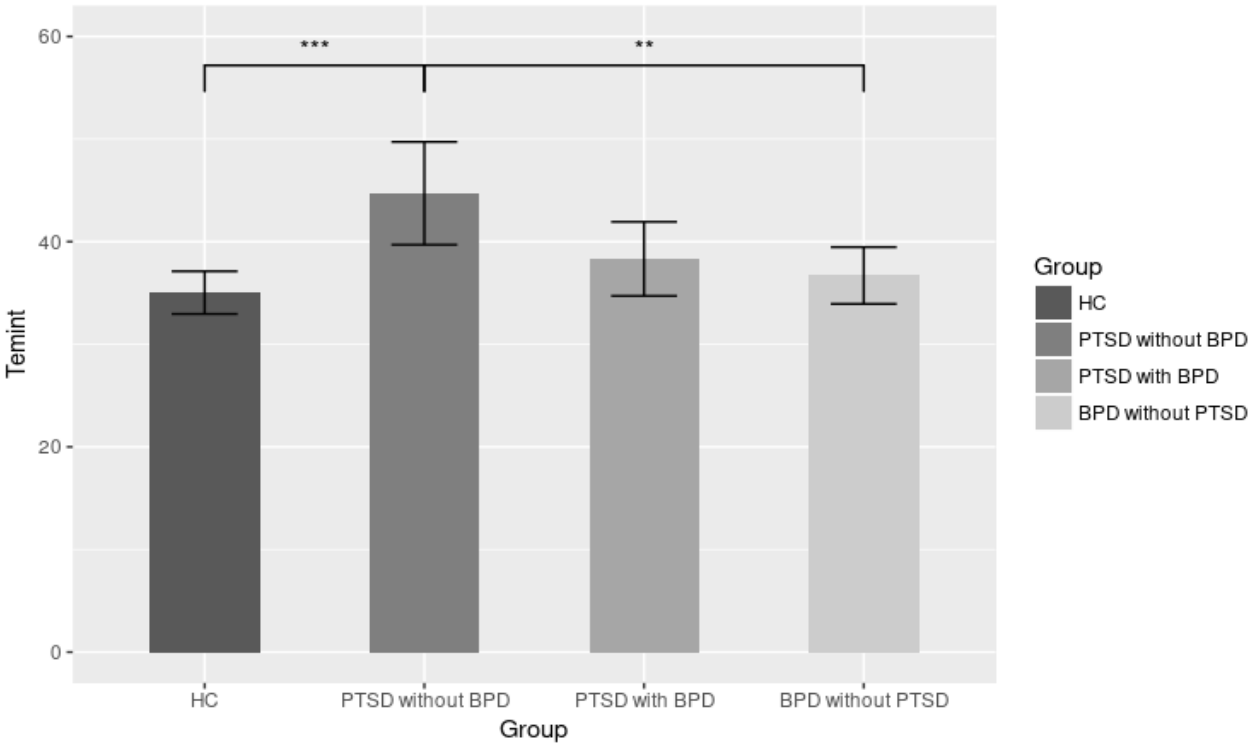
1.5 RESULTS

1.5.1 Study 1: Emotional Intelligence in Patients with Posttraumatic Stress Disorder, Borderline personality disorder, and Healthy Controls.

ANOVA revealed a main group effect (F (3, 167) = 6.9, p < .001). Bonferroni-corrected post hoc analysis showed a significant difference in emotional intelligence between the

PTSD without BPD group and healthy controls (p < .001) with a large effect size (d = .86) as well as between the PTSD without BPD group and the BPD without PTSD group (p = .003) with a medium effect size (d = .65). There were no significant differences in emotional intelligence between all of the other groups.

Fig. 1: Effect of Main Factor Group (HC, PTSD without BPD, PTSD with BPD, BPD without PTSD) on Emotional Intelligence, Based on ANOVA



Note: HC=healthy controls; PTSD=Posttraumatic Stress Disorder; BPD=Borderline Personality Disorder; TEMINT=Test of Emotional Intelligence; confidence intervals (CIs) 95% are represented in the figure by the error bars attached to each column, higher scores indicate lower emotional intelligence; asterisks mark the level of significance **p<.01, ***p<.001.This figure has been published in Janke et al. (2018).

We found a significant effect of the main factor group on the 10 different emotions (T = 0.32, F (30, 527) = 1.88, p < .005) using multivariate analysis of variance (MANOVA) and Hotelling's trace statistics. For seven emotions, we found significant differences of group means in emotional intelligence, these emotions were: “aversion”, “anger”, “fear”, “sadness”, “guilt”, “happiness” and “affection”. Bonferroni-corrected post hoc analysis showed that the difference of group means for these emotions were significant between the PTSD without BPD group and healthy controls. There were no significant group

differences for the emotions “unease”, “pride” and “surprise”. Again, the BPD without PTSD group did not differ significantly from healthy controls.

1.5.2 Study 2: Enhanced Emotional Empathy after Mineralocorticoid Receptor Stimulation in Women with Borderline Personality Disorder and Healthy Women

Using the MET, ANOVA with repeated measurements revealed a main effect of treatment (p = .008) as well as a test score by treatment-interaction effect (p = .01). Emotional empathy was enhanced in the fludrocortisone condition compared to placebo across groups (main effect treatment (F (1, 69) = 7.1, p = .009). There was no significant group effect (F (1, 69) = 2.1, p = .15) or treatment by group interaction effect (F (1, 69) = 0,4, p = .55). This means that patients with BPD did not differ from healthy controls in emotional empathy and that both groups benefitted from fludrocortisone.

The cognitive part of the MET did not reveal any significant differences, meaning there was no significant difference between BPD patients and healthy women in cognitive empathy across treatment modalities.

Separate ANOVAs that analyzed the effects of fludrocortisone on cognitive empathy in the MASC did not reveal significant effects when controlling for potential confounders.

1.5.3 Study 3: Effects of Mineralocorticoid Receptor Stimulation via Fludrocortisone on Memory in Women with Borderline Personality Disorder

Regarding the RCFT (visuospatial memory) ANOVA with repeated measures revealed no significant main effect of group, and no main effect of drug, but, a significant drug by group interaction effect was observed (F (1, 75) = 102.5, p= .03). Post hoc ANOVA for each group showed that fludrocortisone lead to impaired test performance compared to placebo in BPD patients (p=.03) for immediate as well as delayed recall. No drug effect was found in the control group.

ANOVA with repeated measures was conducted to analyze AVLT (verbal memory). It revealed no main effect of group, but a significant drug by group interaction (F (1, 76) = 15.71, p = .03). Fludrocortisone impaired memory performance in BPD compared to placebo (post hoc ANOVA, p = .04), but not in healthy controls.

Two separate ANOVAs with the Digit Span Forward and Backward Task as dependent variables were conducted to analyze working memory performance. A main effect of

drug was revealed for the digit span backward task (F (1, 142) = 4.920, p =.03). Fludrocortisone improved working memory compared to placebo across groups.

1.6 DISCUSSION

We investigated aspects of social cognition and memory function in patients with BPD, BPD with comorbid PTSD, PTSD without BPD and healthy controls and, furthermore, analyzed the influence of MR stimulation with glucocorticoids on these aspects. Results revealed significant impairments in emotional intelligence in patients with PTSD without BPD, which were not specific to PTSD-associated emotions but related to many different emotions including PTSD-associated emotions. We did not find significant impairments in patients with BPD, neither in emotional intelligence nor in emotional or cognitive empathy. Stimulation of MR with fludrocortisone influenced empathy and memory in BPD and healthy controls. It enhanced emotional empathy in patients with BPD and healthy controls but did not influence cognitive empathy. Furthermore, MR stimulation impaired visuospatial and verbal memory in patients with BPD and enhanced working memory in BPD as well as in healthy controls.

In summary, we did not find impairments in emotional intelligence in patients with BPD. This is in line with some studies regarding emotional intelligence and empathy (e.g. Beblo et al., 2010; Jeung & Herpertz, 2014 for review; Peter et al., 2018). Nevertheless, our results stand in contrast to other studies that found impairments in emotional intelligence in BPD (e.g. Hertel et al., 2009; Hurtado et al., 2016; Peter et al., 2013) and in cognitive or emotional empathy (e.g. Anupama et al., 2018; Dziobek et al., 2011; Harari, Shamay-Tsoory, Ravid, & Levkovitz, 2010; Nemeth et al., 2018). This discrepancy could be partly attributed to differing assessment instruments (e.g., different aspects of social cognition, self-report or task-based measures and ecological complexity of the tasks). Furthermore, the heterogeneous BPD symptom severity throughout different studies might account for dissimilar results, especially since one study found a significant correlation between BPD symptom severity and performance in emotional intelligence (Peter et al., 2013). BPD symptom severity of our sample can be classified as moderate since it meets an average of 6.27 of the necessary DSM-IV criteria. Controlling for PTSD in the BPD group, as we have in our study, might serve as another possible explanation. Most of the other studies did not report on that aspect

and, hence, might have overlooked an important confounding variable, as it was demonstrated for social cognition tasks (Duque-Alarcon et al., 2019; Preissler et al., 2010). As mentioned before, performance of patients with BPD in social cognition tasks is influenced by high arousal or emotional states (Sharp et al., 2011), complexity, and ecological validity of the task (Roepke et al., 2012). Since the TEMINT shortly describes situations that persons experience and does not use animated material one could reason that participants of the study are not sufficiently emotionally involved when filling out the form. In addition, the TEMINT does not use very complex or ecologically valid material, which could explain why we did not find differences in emotional intelligence between patients with BPD and healthy controls. On the other hand, MET and MASC, which we use in our studies for measuring emotional and cognitive empathy, are explicitly developed as ecologically valid measures. We did not find significant differences in empathy between BPD and healthy controls using these ecologically valid measures, either. A very recent study replicated our result of no significant difference between BPD and healthy controls in emotional and cognitive empathy, using the MET (Wingenfeld et al., 2018). One review even found empathic enhancements under more socially interactive experimental designs and proposed a combination of high attention to social stimuli and dysfunctional social information processing to explain the "borderline empathy paradox" (Dinsdale & Crespi, 2013).

Impairments in social cognition are reported for patients with BPD with comorbid PTSD using the MASC (Preissler et al., 2010). On these grounds, another finding to discuss, is, why patients with BPD with PTSD do not differ significantly from healthy controls in emotional intelligence in our sample. One possible explanation could be a relatively small sample size in the BPD with comorbid PTSD group, which limits statistical power. Furthermore, making misdiagnoses should be taken into consideration. Since PTSD and BPD share common characteristics like dissociations or hyperarousal, overdiagnosing PTSD in the BPD with PTSD group seems like a reasonable possibility. Another point to take into account is an altered use of coping strategies in different groups. While the PTSD only group most likely uses avoidance strategies (Olff, Langeland, & Gersons, 2005), this might not be the case for the group of patients with BPD with comorbid PTSD.

The demonstrated impairments in emotional intelligence in PTSD resonate with other findings of deficits in social cognition in PTSD, e.g., theory of mind and empathy (Mazza et al., 2012; Mazza et al., 2015; Nazarov et al., 2014; Schmidt & Zachariae, 2009; Stevens & Jovanovic, 2019). It remains unclear whether this deficit in social cognition can be interpreted in terms of an underlying deficit (Sharp et al., 2012) or as core symptomology of PTSD. Core symptoms that could have an impact on social cognition in PTSD are cognitive biases (Woud, Verwoerd, & Krans, 2017), severity of dissociations (Nazarov et al., 2015; Nazarov et al., 2014), or neurocognitive deficits (Sumner et al., 2017). However, patients with BPD also suffer from these symptoms and they did not display significant deficits in emotional intelligence in our study.
Concerning the hypothesis of impairments in PTSD-associated emotions, we found patients with PTSD having impairments in many different emotions that were not limited to, but included PTSD-associated emotions. Only “unease”, “surprise” and “pride” were unaffected by these impairments, which may be due to their relatively unspecific valence.

According to effects of MR stimulation on social cognition in women with BPD and healthy controls, we found enhanced emotional empathy in both groups, which is in line with our hypothesis. Since MR are expressed in limbic brain structures and are involved in appraisal processes related to the onset of stress reactions (de Kloet, 2013), it is plausible that they are involved in processing emotional information. The role of MR in emotional processing has already been demonstrated (Schultebraucks et al., 2016). It remains unclear, however, why MR stimulation only had a significant effect on emotional but not on cognitive empathy. A very recent study found a differential effect of a psychosocial stressor on emotional empathy in BPD (Wingenfeld et al., 2018), which strengthens our findings. The possibility to be able to enhance emotional empathy through MR stimulation with fludrocortisone in BPD offers important clinical implications. MR stimulation could be implemented into psychotherapeutic settings to strengthen therapeutic alliance and to optimize learning effects.

Regarding the influence of MR stimulation on cognition, we found, in line with our hypothesis, an improved performance in working memory in the fludrocortisone condition compared to placebo across groups. Nevertheless, contrary to our hypothesis, we found impairments in visuospatial and verbal memory in patients with BPD after MR

stimulation with fludrocortisone. This is clearly in contrast to the results of healthy controls that showed an improvement in cognition after fludrocortisone administration (see de Kloet et al., 2016 for review; Hinkelmann et al., 2015; Otte et al., 2015; Piber et al., 2016). It seems as if the effects of fludrocortisone on cognition in BPD are very heterogeneous and subject to the investigated cognitive domain and involved brain region. Our study shows first evidence that hippocampus-associated memory (e.g., verbal and visuospatial memory) could be negatively effected through MR stimulation in BPD. PFC dependent memory (e.g., working memory), on the other hand, seems to be positively effected through MR stimulation. Since structural brain data show smaller hippocampus volume in BPD (Wingenfeld et al., 2010), it is conceivable that differences between BPD and healthy controls can be explained by hippocampal MR alterations in BPD. It warrants further studies to replicate the findings of impairing effects of fludrocortisone stimulation on hippocampus-based memory but enhancing effects on working memory and emotional empathy in BPD. Even more so, since the field of investigation on the role of MR stimulation in human is relatively new and important moderating effects of age and sex have not been figured out so far.

There are several strengths of our studies. First, all patients were diagnosed by trained clinical psychiatrists or psychologists with structured clinical interviews (M.I.N.I. or SCID-I and SCID-II). Another strength of the MR stimulation studies is the placebo-controlled design with randomized participants in the second study and the placebo-controlled, within-subject, cross-over study design in the third study. They have been the first studies examining the effects of MR stimulation on social cognition in humans and on visuospatial memory, verbal memory, and working memory in women with borderline personality disorder via fludrocortisone. There are also some limitations of our studies calling for further investigations. First, our results are restricted to women and need to be replicated with men. For measurement of emotional intelligence, we used the common instrument TEMINT. In addition, other instruments could serve helpful to detect emotions like shame or disgust, which are common in PTSD patients as well as in BPD. Since our sample of patients with PTSD with BPD and PTSD only was exposed to repeated interpersonal traumatic events, it would be interesting to examine patients with PTSD after mono-traumatic and accident-related traumatic events, as they may display a different set of impairments. In our MR stimulation studies, we did not control for menstrual cycle phase, though the intake of oral contraceptives had no

influence on the results. Additionally, further studies should include other measures of social cognition.

In summary, patients with BPD did not display deficits in the investigated aspects of social cognition (emotional intelligence, emotional and cognitive empathy). Patients with PTSD without comorbid BPD did display deficits in emotional intelligence, affecting a wide range of emotions. Possible reasons for conflicting results regarding social cognition in BPD have been discussed as well as possible interpretations of findings regarding impaired emotional intelligence in PTSD without BPD. Stimulating the MR with fludrocortisone, we found enhanced emotional empathy in patients with BPD and healthy controls compared to the placebo condition, but no influence on cognitive empathy. Furthermore, stimulation of the MR with fludrocortisone led to impaired visuospatial and verbal memory in patients with BPD and enhanced working memory in BPD as well as in healthy controls compared to placebo. Hippocampal MR alterations in BPD are proposed to explain task-related findings of MR stimulation in BPD. Future studies are warranted to address the unanswered questions regarding aspects of social cognition in patients with BPD with and without comorbid PTSD.

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2. EIDESSTATTLICHE VERSICHERUNG (STATEMENT OF AUTHORSHIP)

„Ich, Katrin Janke, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Aspects of Social Cognition and Memory in Patients with Borderline Personality Disorder“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen werden von mir verantwortet.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

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Datum Unterschrift

3. AUSFÜHRLICHE ANTEILSERKLÄRUNG (AUTHORSHIP CONTRIBUTION STATEMENT)

Katrin Janke hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: Janke, K., Driessen, M., Behnia, B., Wingenfeld, K., Roepke, S., Emotional intelligence in patients with posttraumatic stress disorder, borderline personality disorder and healthy controls. Psychiatry Res 264, 290-296, (2018). Impact Factor (2017): 2.223

Bei der Erstellung der Publikation war ich maßgeblich bei der Planung und Ausarbeitung der Studie beteiligt. Ich unternahm die Rekrutierung der Patienten und die Datenerhebung (Durchführung der klinischen Interviews SKID 1 und SKID 2 sowie Instruktion der Patienten zur Fragebogenerhebung des TEMINTs und der begleitenden psychometrischen Tests wie PDS, BDI, CTQ etc.). Ich führte die statistische Auswertung mittels SPSS Version 22.0 durch. Dies beinhaltete die Vorverarbeitung der Daten (Umgang mit fehlenden Werten und mit Ausreißern, Bildung von Gruppenvariablen etc. sowie die Durchführung der Datenanalyse bzgl. der Gesamtstichprobe). Zudem erstellte ich die Abbildung mithilfe von R. Außerdem fertigte ich die Erstfassung des Manuskripts an, arbeitete die Anmerkungen der Co-Autoren ein und erstellte somit die Endfassung des Manuskripts. Die Überarbeitung des Manuskripts im Rahmen des Review Prozesses unter Berücksichtigung der Anmerkungen der Reviewer führte ich ebenfalls durch. Eng unterstützt und supervidiert wurde ich bei den einzelnen Schritten von Prof. Stefan Röpke.

Publikation 2: Wingenfeld, K., Kuehl, L.K., **Janke, K.,** Hinkelmann, K., Dziobek, I., Fleischer, J., Otte, C., Roepke, S., Enhanced emotional empathy after mineralocorticoid receptor stimulation in women with borderline personality disorder and healthy women. Neuropsychopharmacology 39 (8), 1799-1804, (2014). Impact Factor (2017): 6.544

Bei der Erstellung der Publikation war ich maßgeblich bei der Rekrutierung der Patienten und teilweise bei der Datenerhebung (Durchführung des MINI und SKID 2) beteiligt. Ich unterstützte bei der weiteren Datenerhebung durch Organisation und Koordination der Untersuchungstermine. Ich verfasste zudem Anmerkungen zum

Manuskript und half bei der Überarbeitung des Manuskripts im Rahmen des Review Prozesses unter Berücksichtigung der Anmerkung der Reviewer.

Publikation 3: Wingenfeld, K., Kuehl, L.K., **Janke, K.,** Hinkelmann, K., Eckert, F.C., Roepke, S., Otte, C., Effects of mineralocorticoid receptor stimulation via fludrocortisone on memory in women with borderline personality disorder. Neurobiol Learn Mem 120, 94-100, (2015). Impact Factor (2017): 3.244

Bei der Erstellung der Publikation war ich maßgeblich bei der Rekrutierung der Patienten und teilweise bei der Datenerhebung (Durchführung des MINI und SKID 2) beteiligt. Ich unterstütze bei der weiteren Datenerhebung durch Organisation und Koordination der Untersuchungstermine. Ich verfasste zudem Anmerkungen zum Manuskript und half bei der Überarbeitung des Manuskripts im Rahmen des Review Prozesses unter Berücksichtigung der Anmerkung der Reviewer.

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Unterschrift der Doktorandin

4. DRUCKEXEMPLARE DER AUSGEWÄHLTEN PUBLIKATIONEN (PRINT EDITION OF THE SELECTED PUBLICATIONS)

Janke, K., Driessen, M., Behnia, B., Wingenfeld, K., Roepke, S., 2018. Emotional intelligence in patients with posttraumatic stress disorder, borderline personality disorder and healthy controls. Psychiatry Res 264, 290-296. https://doi.org/10.1016/j.psychres.2018.03.078

Wingenfeld, K., Kuehl, L.K., Janke, K., Hinkelmann, K., Dziobek, I., Fleischer, J., Otte, C., Roepke, S., 2014. Enhanced emotional empathy after mineralocorticoid receptor stimulation in women with borderline personality disorder and healthy women. Neuropsychopharmacology 39 (8), 1799-1804. https://doi.org/10.1038/npp.2014.36

Wingenfeld, K., Kuehl, L.K., Janke, K., Hinkelmann, K., Eckert, F.C., Roepke, S., Otte, C., 2015. Effects of mineralocorticoid receptor stimulation via fludrocortisone on memory in women with borderline personality disorder. Neurobiol Learn Mem 120, 94-100. Impact Factor (2017): 3.244. https://doi.org/10.1016/j.nlm.2015.02.013

5. CURRICULUM VITAE

My curriculum vitae does not appear in the electronic version of my dissertation for reasons of data protection.

6. LIST OF PUBLICATIONS

Janke, K., Driessen, M., Behnia, B., Wingenfeld, K., Roepke, S., 2018. Emotional intelligence in patients with posttraumatic stress disorder, borderline personality disorder and healthy controls. Psychiatry Res 264, 290-296. Impact Factor (2017): 2.223

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Book chapter:

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