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Impact of stress on memory and empathy in patients with a borderline personality disorder and healthy controls

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ENGLISH SUMMARY

The borderline personality disorder (BPD) comprises a wide variety of symptoms related to emotional dysregulations and impairments in social interactions which potentially culminate in suicidal behavior. In addition, one core feature of the BPD symptomatology is a dysfunctional stress-regulation. However, so far studies investigating the physiology of the stress-system in BPD revealed heterogeneous results. Furthermore, empirical evidence shows that in healthy individuals, stress influences higher cognitive abilities like the memory-system. Although BPD patients are known to experience stress on a daily basis, little is known about a possible connection to their memory performance. The few available data rather suggest enhanced memory after stress in BPD patients, which is remarkable since stress robustly impairs memory performance in healthy individuals. Moreover, stress often appears in conflict-riddled situations, but empirical evidence about a possible relation between the stress-system in BPD and social interactional skills is again almost non-existent. Finally, research over the last decades used a comprehensive variety of laboratory stressors (from simulated job interviews to synthetic stress hormones) to detect the influence of the endogenous stress response or a single receptor activation through a pharmacological approach on memory in healthy individuals. These evidence account for important insight in different stress-receptor systems. However, data about the impact of single stress hormones on social skills in healthy individual are rare but needed to subsequently disentangle receptor functions.

The object of this dissertation is to extend existing knowledge about the physiological stress-system in BPD patients and its possible impact on memory on the one hand and social interactional skills on the other hand. Of note, the vast majority of studies, which investigated in BPD so far tested female patients, which also accounts for this dissertation. To further close another research gap in this field, the impact of a single stress hormone on social interactional skills in healthy males and females will be investigated. Thus, this dissertation project comprises four research questions:

Q-I: How does an acute psychosocial stressor influences the physiological stress-system in female BPD patients, compared to a placebo-condition and compared to female healthy controls?

Q-II: How does psychosocial stress impact on the memory performance in female patients with a borderline personality disorder compared to a placebo-condition and compared to female healthy controls?

Q-III: How does psychosocial stress affect empathy in female patients with a borderline personality disorder compared to a placebo-condition and compared to female healthy controls?

Q-IV: Does pharmacologically administered cortisol modulate facial emotion recognition and empathy in healthy young men and women?

In a nutshell, the main results of this dissertation are as follows: First, female BPD patients showed a blunted physiological stress reaction to a well-established psychosocial stressor, compared to female healthy controls. Second, the provoked stress response had no impact on the memory performance in female BPD patients, compared to the placebo-condition. Furthermore, the stress response also had no impact on memory in HC and there were only few differences in memory performance between BPD and HC. Third, the provoked stress response differently influenced empathy in BPD and HC. Empathy comprises two parts, cognitive and emotional empathy. After acute stress female BPD patients showed significantly lower scores compared to HC. Post-hoc tests showed no significant differences for emotional empathy between stress and the placebo-condition in both groups. Cognitive empathy was unaffected by stress in BPD and HC. Finally, the synthetic stress hormone cortisol had no impact on empathy in healthy individuals. The ability to detect emotional expressions in faces was only affected by stress for subtle emotions and was sex specific. However, no main effect of cortisol on facial emotion recognition was found.

To conclude, the present findings extend and partly confirm the empirical evidence for an altered stress-system in female BPD patients. At the same time and in concert with the results

regarding the impact of stress on memory and interactional skills, the data show the need for a more complex model to correctly interpret the findings. Thus, on the one hand this dissertation imbeds the results about an altered stress physiology in an etiological model comprising gene by environment interactions (G X E) rather than BPD symptomatology. On the other hand, the impact of stress on higher cognition (memory and social skills) is interpreted against the background of the G X E consequences in BPD.

DEUTSCHE ZUSAMMENFASSSUNG (GERMAN SUMMARY)

Patienten mit einer Borderline-Persönlichkeitsstörung (BPS) haben häufig große Schwierigkeiten bei der Regulation ihrer Gefühle und erleben enge soziale Beziehungen als herausfordernd bis konfliktreich. Diese Gefühle können sich bis zu suizidalem Verhalten steigern. Zudem zeigen BPS-Patienten eine veränderte Stressregulation, wobei die aktuelle Studienlage zur physiologischen Stressreaktion bei dieser Patientengruppe heterogen ist. Bei gesunden Versuchspersonen konnte wiederholt gezeigt werden, dass Stress das Gedächtnis beeinflusst. Obwohl BPS-Patienten möglicherweise eine veränderte physiologische Stressreaktion haben, finden sich kaum Studien, die diesen Zusammenhang untersuchen. Vorhandene Daten zeigen eher eine Verbesserung des Gedächtnisses nach Stress bei BPS-Patienten, was bemerkenswert ist, da Stress bei gesunden Probanden zuverlässig eine Gedächtnisverschlechterung bewirkt. Wie erwähnt, erleben BPS-Patienten ihre Beziehungen und allgemein soziale Interaktionen als konfliktreich. Da soziale Situationen auch mit erlebtem Stress einhergehen können, stellt sich weiterhin die Frage, ob es bei BPS einen Zusammenhang zwischen dysfunktionalen sozialen Interaktionen und dem Stresssystem gibt. Auch hierzu gibt es bisher wenig Befunde. Um eine Stressreaktion im Labor zu erzeugen, wurden bisher diverse Methoden angewandt. Diese reichen von synthetischen Stresshormonen bis zu simulierten Bewerbungsgesprächen, um die körpereigene Stressreaktion zu aktivieren. Durch zahlreiche Anwendungen verschiedener Methoden konnte der Einfluss von Stress auf das Gedächtnis bis heute immer besser verstanden werden. Ein Blick in die Literatur zeigt allerdings, dass der Einfluss von Stress auf soziale Fähigkeiten bei Gesunden weniger umfassend untersucht wurde. Das erscheint aber notwendig, um auch in diesem Bereich verschiedene Stresssysteme und Rezeptorfunktionen zu verstehen.

Gegenstand dieser Dissertation ist es, das physiologische Stresssystem bei BPS-Patienten zu untersuchen und eine potenzielle Veränderung gegenüber gesunden Probanden aufzuzeigen.

Darüber hinaus soll der Einfluss der im Labor provozierten Stressreaktion auf das Gedächtnis und auf soziale Fähigkeiten bei BPS-Patienten im Vergleich zu einem Placebo und im Vergleich zu Gesunden im Fokus stehen. Es ist wichtig zu erwähnen, dass die meisten bisherigen Studien mit BPS-Patientinnen durchgeführt wurden, was auch für die vorliegende Dissertation gilt. Da es bisher wenige Untersuchungen zum Einfluss eines synthetischen Stresshormons auf soziale Fähigkeiten bei gesunden Männern und Frauen gibt, stellt diese Fragestellung den Abschluss der Dissertation dar. So ergeben sich insgesamt vier Forschungsfragen:

F-I: Zeigen BPS-Patientinnen eine veränderte physiologische Stressreaktion in Bezug auf einen psychosozialen Laborstressor (simuliertes Bewerbungsgespräch) im Vergleich zu einer nicht stressigen Placebo-Situation und im Vergleich zu gesunden Probandinnen?

F-II: Wie beeinflusst ein psychosozialer Stressor das Gedächtnissystem von BPS-Patientinnen im Vergleich zu einer Placebo-Situation und im Vergleich zu gesunden Probandinnen?

F-III: Wie beeinflusst ein psychosozialer Stressor die Empathie von BPS-Patientinnen im Vergleich zu einer Placebo-Situation und im Vergleich zu gesunden Probandinnen?

F-IV: Wird Empathie und die Fähigkeit, Emotionen in Gesichtern zu erkennen bei gesunden Männern und Frauen durch die Gabe eines Stresshormones beeinflusst?

Die Hauptergebnisse der Dissertation sind wie folgt: Erstens, BPS-Patientinnen zeigen im Vergleich zu gesunden Probandinnen eine abgeschwächte physiologische Stressreaktion bezogen auf einen psychosozialen Laborstressor. Zweitens, die induzierte Stressreaktion hatte keinen Einfluss auf das Gedächtnissystem bei BPS-Patientinnen im Vergleich zu einer Placebo-Situation. Auch bei den gesunden Probandinnen hat der Stress das Gedächtnis nicht beeinflusst. Darüber hinaus unterschieden sich gesunde Probandinnen und BPS-Patientinnen nur marginal in Bezug auf die Gedächtnisleistung. Drittens, die induzierte Stressreaktion hat die Empathiefähigkeit bei Frauen mit BPS und bei den gesunden Frauen unterschiedlich beeinflusst. Empathie besteht aus mindestens

zwei Komponenten, emotionaler und kognitiver Empathie. Die BPS-Patientinnen zeigten nach Stress signifikant geringere Werte für emotionale Empathie im Vergleich zu den gesunden Probandinnen. Der post-hoc Vergleich zwischen Stress und Placebo wies allerdings keine Unterschiede für Empathie nach, sowohl für BPS-Patientinnen als auch für gesunde Frauen. Kognitive Empathie wurde durch die induzierte Stressreaktion nicht beeinflusst. Viertens, synthetisches Cortisol hatte keinen Einfluss auf die Empathie bei gesunden Probanden. Die Fähigkeit Emotionen in Gesichtern zu erkennen, war durch Stress nur beeinflusst für subtil gezeigte Emotionen und der Einfluss war geschlechtsspezifisch. Es konnte allerdings auch hier kein Haupteffekt des Hydrocortisons gefunden werden.

Zusammengefasst bestätigen die vorliegenden Befunde einerseits, dass BPS-Patientinnen eine veränderte physiologische Stressreaktion haben. Gleichzeitig, und mit Blick auf die Ergebnisse zum Gedächtnis und zu den sozialen Fähigkeiten, wird die Notwendigkeit eines komplexeren Erklärungsmodells für die Ergebnisse deutlich. Die Befunde werden demnach in ein ätiologisches Modell eingeordnet, das sich weniger auf BPS-typische Symptome bezieht, sondern eine Gen-Umwelt-Interaktion als Grundlage hat.

1. THEORETICAL AND EMPIRICAL BACKGROUND

The borderline personality disorder (BPD) is an overarching condition comprising an unstable sense of identity, lack of interpersonal skills, (self-destructive) impulsive behavior and emotional dysregulation (American Psychiatric Association, 2013 (APA)). One core feature of the BPD is an altered stress regulation, which is often suggested to play a critical moderating role in the complex symptomatology (Lazarus, Cheavens, Festa, & Zachary Rosenthal, 2014). Since BPD patients are highly sensitive to environmental and interpersonal triggers respectively, the daily routine can become like running the gauntlet. Even little events are capable of activating stress, harm and dysfunctional cognitions, which can end up in feelings of desperateness and eventually suicidal behavior (Gunderson, Herpertz, Skodol, Torgersen, & Zanarini, 2018). Research over the last decades confirm that BPD patients not only show a dysregulation in their subjective perception of stress, but also an altered stress physiology (e.g. Aleknaviciute et al., 2016; Drews, Fertuck, Koenig, Kaess, & Arntz, 2018; Nater et al., 2010; Rinne et al., 2002). However, results across studies are still heterogeneous and more insight is needed to clarify how a dysfunctional stress physiology contributes to the symptomatology. Moreover, acute stress can directly and indirectly act on the brain via stress hormones and neurotransmitters and in turn on cognitive functions (e.g. Wolf, 2009; Wolf, 2017). Interestingly, for healthy controls (HC) there is robust evidence that acute stress enhances the formation of new memory traces, whereas the retrieval of information is impaired (Schwabe, 2017; Schwabe, Joëls, Roozendaal, Wolf, & Oitzl, 2012). Remarkably, while stress seems to be a constant factor in BPD symptomatology, evidence for an impact of experienced stress on memory is almost non-existent and the few available data implicate rather contrasting effects compared to HC (e.g. Wingenfeld et al., 2013). Other core features of the BPD are dysfunctional relationships and altered social interactional skills (Lazarus, Cheavens, Festa, & Rosenthal, 2014; Roepke, Vater, Preißler, Heekeren, & Dziobek, 2013). However, studies are heterogeneous in

matters of social cognitive skills in BPD patients, since some found enhanced and others revealed diminished abilities (Dinsdale & Crespi, 2013; Roepke et al., 2013). In research, these symptoms are often suggested to be influenced by or connected to perceived stress in social situations, which might explain diverging results (Jeung & Herpertz, 2014; Lazarus, Cheavens, Festa, & Rosenthal, 2014). However, again rather little is known about a clear impact of acute stress on social cognitive abilities in BPD. Hence, stress might be an important moderating factor for other BPD related symptoms but to date little is known about these connections. Finally, literature indicates that a comprehensive variety of naturalistic stressors and synthetic stress hormones is used to detect and disentangle their impact on memory performance in healthy controls (e.g. de Quervain, Schwabe, & Roozendaal, 2016; de Quervain, Aerni, Schelling, & Roozendaal, 2009; Wolf, Atsak, De Quervain, Roozendaal, & Wingenfeld, 2016). However, results for the impact of stress on social cognition in healthy individuals are mainly based on naturalistic stressors within the laboratory. The effects of a single stress-hormone administration on social skills are rare but needed to separate different stress hormone and neurotransmitter influences on interactional abilities and to compare healthy controls and patient with mental disorders.

Together, the above-mentioned gaps in research lead to the relevance of this dissertation: The first object is to gain further insight into the physiological stress reaction in BPD patients compared to a placebo-condition and to healthy controls. Therefore, section 1.1 provides a short overview of the symptomatology and etiology of the BPD, followed by a summary about stress and its definition (1.2). Next, the two main physiological stress axes and current evidence for their alterations in BPD will be specified in the sections 1.2.1 to 1.2.2. The second object is to shed more light on the impact of acute stress on the memory system in BPD and compare results to a placebo-condition and a group of healthy individuals. Thus, section 1.3 comprises information about the memory system in general and subsequently about the current empirical background about the impact of stress on

memory in BPD patients and HC. The third object is to investigate a possible impact of a stressful situation on social cognitive abilities in BPD patients and again compare the results to a placebo-condition and to HC. Therefore, section 1.4 illustrates a short summary on important social cognitive concepts and subsequently, existing studies on the impact of stress on social cognitive abilities in BPD patients are summarized in section 1.4.1 Finally, and as outlined above, literature indicates that data on the impact of a single stress hormone on social cognitive abilities in HC are missing. Thus, the fourth object of this dissertation project is to dispense a synthetic stress hormone to a population of healthy individuals and test potential changes on social cognitive abilities compared to a placebo. Information about current empirical evidence about the impact of stress on social cognition in HC is given in section 1.4.3.

However, before we delve into these objects, we start with an overview about BPD and a short history about stress.

1.1. BORDERLINE PERSONALITY DISORDER

The borderline personality disorder (BPD) was first described by Stern (1938) and is a severe mental disorder, whose prevalence rate is about 1.7% (Gunderson et al., 2018) in the general population, which appears to be approximately 10 % of all psychiatric outpatients and 15-28 % of all psychiatric inpatients (Cattane, Rossi, Lanfredi, & Cattaneo, 2017; Gunderson et al., 2018). Although the ratio of BPD in the general population seems not to differ between men and women, the ratio of the clinical population is about 3:1 in favor of female patients (Chapman, Jamil, & Fleisher, 2019). Therefore, the vast majority of conducted studies, and which are cited in this dissertation tested female BPD patients. Including this dissertation. The BPD is characterized by an overarching instability in stress management, affect regulation, sense of self, impulse control and

interpersonal relationships. These patterns often result in aggressive and impulsive behavior, intense conflicts, fear of abandonment, volatile emotionality and dysfunctional cognitions, which sometimes culminate in chronic suicidal tendencies and self-harming behavior (Gunderson et al., 2018; Paris, 2018). Besides a sensitivity to react rapidly and impulsively to environmental and interpersonal triggers, BPD patients are also known to suffer from a slow return to baseline, which makes it even more difficult to cope with even slightly stressful events (Eddie et al., 2018). The most established aetiopathological theory for the development of BPD suggests an interaction between biological and psychological factors (Linehan, 1993). Biological factors comprise a higher vulnerability and stress sensitivity, potentially based on genetics (Gunderson et al., 2018). The most commonly described psychological factor seems to be childhood trauma (CT) during critical developmental phases (Leichsenring, Leibing, Kruse, New, & Leweke, 2011). Literature shows that several terms and definitions are used to describe adverse childhood experiences (ACE). Therefore, in this dissertation the abbreviation CT/ACE will be used as a synonym to face different terms in literature. Leeb, Paulozzi, Melanson, Simon, and Arias (2008) provide a comprehensive explanation and define CT/ACE as *'Any act or series of acts of commission or omission by a parent or other caregiver that results in harm, potential for harm, or threat of harm to a child'*. The authors further postulate that physical, sexual and psychological abuse are acts of commission (child abuse), whereas acts of omission (child neglect) imply '*The failure to provide for a child's basic physical, emotional, or educational needs or to protect a child from harm or potential harm.'* The above definition shows that childhood trauma (CT) or adverse childhood experiences (ACE) (Brown et al., 2009) can comprise a single event or long-lasting periods of constant disruptive care takers behavior or neglect. Research indicates that experiencing CT/ACE can exceed the individuals resilience and can results in permanent elevated stress levels (Pechtel & Pizzagalli, 2011).

Chronically elevated stress during childhood is suggested to program neuronal function to adapt an individual to its aversive environment, and subsequently alters responsiveness and feedback sensitivity of important stress regulation mechanisms (Agorastos, Pervanidou, Chrousos, & Kolaitis, 2018; Oitzl, Champagne, van der Veen, & de Kloet, 2010). Interestingly, up to 90 % of the BPD population report on a wide variety of acts of commission and omission and research confirms a relation between BPD symptomatology and CT/ACE (Gunderson et al., 2018; Zanarini et al., 1997; Zanarini et al., 2002). Since CT/ACE seems to play a critical role in BPD and has the potential to change an individual's stress physiology, the next section provides an overview about stress and its neuroendocrinological response systems, followed by a summary of existing data on alterations of the stress-system in BPD.

1.2. STRESS

The daily life comprises a variety of potential threatening situations and for a human being it is essential that its organism can rapidly provide energy to react to danger and get access to effective coping strategies. On the other hand, reversing the provoked stress response and process the experienced situation is just as important, since a downregulation prevents the organism from damage due to long lasting exposure to stress hormones (e.g. McEwen, Nasca, & Gray, 2016). This restoration of an inner balance was first described by Walter Cannon (1939) who called this concept *homeostasis*. *Homeostasis* refers to the retention of physiological stability within organisms by adapting several internal variables in defined and fixed ranges of values. In this context, Cannon subsequently described the activation of the *autonomic-nervous-system (ANS)* and the release of catecholamines (e.g. adrenalin and noradrenaline) as an adaptive response to an external stressor and thus, the attempt to restore *homeostasis* (Cannon, 1939). Hans Selye, in turn showed that

different stressors always cause a similar physiological response, or rather, a hormonal cascade and linked his findings to the *hypothalamic-pituitary-adrenal (HPA) axis* and the release of glucocorticoids (e.g. cortisol). The HPA axis turned out to be the second important adaptive system in terms of stress. His definition of stress as a *"non-specific response of the body to any demand"* becomes comprehensible and is still valid in many circumstances (Selye, 1936, 1976). Based on these insights, Sterling and Eyer (1988) extended the concept of *homeostasis* by stating that some physiological systems adapt the body to the environment by shifting the setpoint of a variable rather than restoring the amplitude to a fixed index value. They called their concept *allostasis* and depicted the hormones and neurotransmitters of the HPA axis and the autonomic-nervous-system (ANS) as important mediators to obtain physiological balance. In addition, differently to *homeostasis, allostasis* not only refers to local feedback, but involves the entire brain-body complex (McEwen & Stellar, 1993; Sterling & Eyer, 1988). This underlines the assumption that the body's inner balance cannot only be challenged by direct physiological changes through e.g. blood loss but is also closely linked to cognitive processes. In this context, Lazarus and Folkman (1987) postulated two appraisal processes: *Homeostasis* is endangered if an individual appraises a situation as threatening and subsequently its own coping mechanisms as being insufficient to successfully handle the situation. In addition, it is known that a rise of stress hormones in high frequencies and over a long period of time, can cause damage within the brain and body (Cool & Zappetti, 2019), respectively, and might change hormonal responses to stress (Danese & McEwen, 2012). This phenomenon was characterized as *allostatic load* (McEwen, 2002; McEwen & Stellar, 1993) and potentially closes the circle to neuroendocrinological changes in BPD due to CT/ACE. The next sections provide a closer look on the neuronal and neuroendocrine functions of the ANS and the HPA axis and the current knowledge about their alterations in BPD patients.

1.2.1. Stress related neuronal and endocrinological structures

The section above shows that the appraisal of a situation as being threatful is based on individual experiences in the past and current information, which makes it highly subjective. The link between the actual event and past experiences is predominantly moderated by the prefrontal cortex (PFC) and limbic structures, namely the hippocampus and the amygdala (Schwabe & Wolf, 2013). The PFC is known to mainly process executive functions, decision making, working memory and moderates the regulation of a stress response (Domenech & Koechlin, 2015). The hippocampus in turn processes contextual and episodic memory formation and also supports the regulation of a stress response (Tulving & Markowitsch, 1998). The amygdala, in turn is also involved in memory processes but predominantly in processing emotional reactions, arousal and the upregulation of a stress response (Cahill, Babinsky, Markowitsch, & McGaugh, 1995; McEwen & Gianaros, 2010; Phelps, 2004). All these neuronal areas are highly interconnected, and a successful processing of an event is based on an intact interplay (McEwen & Gianaros, 2010). Furthermore, the PFC, the hippocampus and the amygdala are connected to the hypothalamus, which represents a core cerebral region in the regulation of an organism's physiological stress response (Schwabe & Wolf, 2013). The next sections focus on the HPA axis and the ANS and their connection to the hypothalamus and other brain sites. Subsequently, current knowledge about alterations in the stress axes of BPD patients is presented.

1.2.1.1. The autonomic nervous system (ANS)

The autonomic nervous system comprises two parts, the sympathetic and the parasympathetic branch which together modulate the fastest response to a potentially threatening situation (Phillips & Ower, 2019). If homeostasis is jeopardized sympathetic preganglionic neurons in the spinal cord

are activated via the hypothalamus and project to the adrenal medulla and peripheral organs (De Kloet, Joëls, & Holsboer, 2005; Ulrich-Lai & Herman, 2009). Consequently, the catecholamines adrenaline and noradrenaline are released, quickly rise within the brain and the body and return to baseline approximately after one hour (Krugers, Karst, & Joels, 2012). These catecholamines bind to specific membrane-bound adrenoceptors, identified as α- and β-receptors, which, amongst other processes, mediate the stress response and are also prominent in limbic structures and the PFC (Gibbs & Summers, 2002; Roozendaal, McEwen, & Chattarji, 2009). Adrenaline is primarily released from the adrenal medulla and indirectly acts on the brain via peripheral β-receptors located on afferent neuronal traces (e.g. nucleus tractus solitarius) affecting the amygdala and the hippocampus (Roozendaal et al., 2009). In contrast, noradrenaline is not only released by the adrenal medulla but predominantly liberated from the locus coeruleus and other brainstem sites and can act as a hormone and as a neurotransmitter nearby the limbic system (Krugers et al., 2012; McGaugh, 2004; Schwabe et al., 2012; Valentino & Van Bockstaele, 2008). As a result of sympathetic activation, the so called "*fight-or-flight"* response is mobilized, which comprises increased heart rate and blood pressure and a shift of attention to the threat inducing event (Cannon, 1939).

The parasympathetic backlash also occurs following a stressor and modulates the sympathetic reaction mainly via the vagus nerve, which is the tenth of twelve main cerebral nerves and emerges from the medulla oblongata. The efferent fibers of the vagus nerve innervate inner organs like the lungs and the heart and afferent fibers terminate on the nucleus tractus solitarius (NTS). The NTS in turn primarily connects to the amygdala, the hypothalamus and the locus coeruleus to modulate the stress response (Berthoud & Neuhuber, 2000; Breit, Kupferberg, Rogler, & Hasler, 2018). Figure one shows a schematic characterization of the ANS.

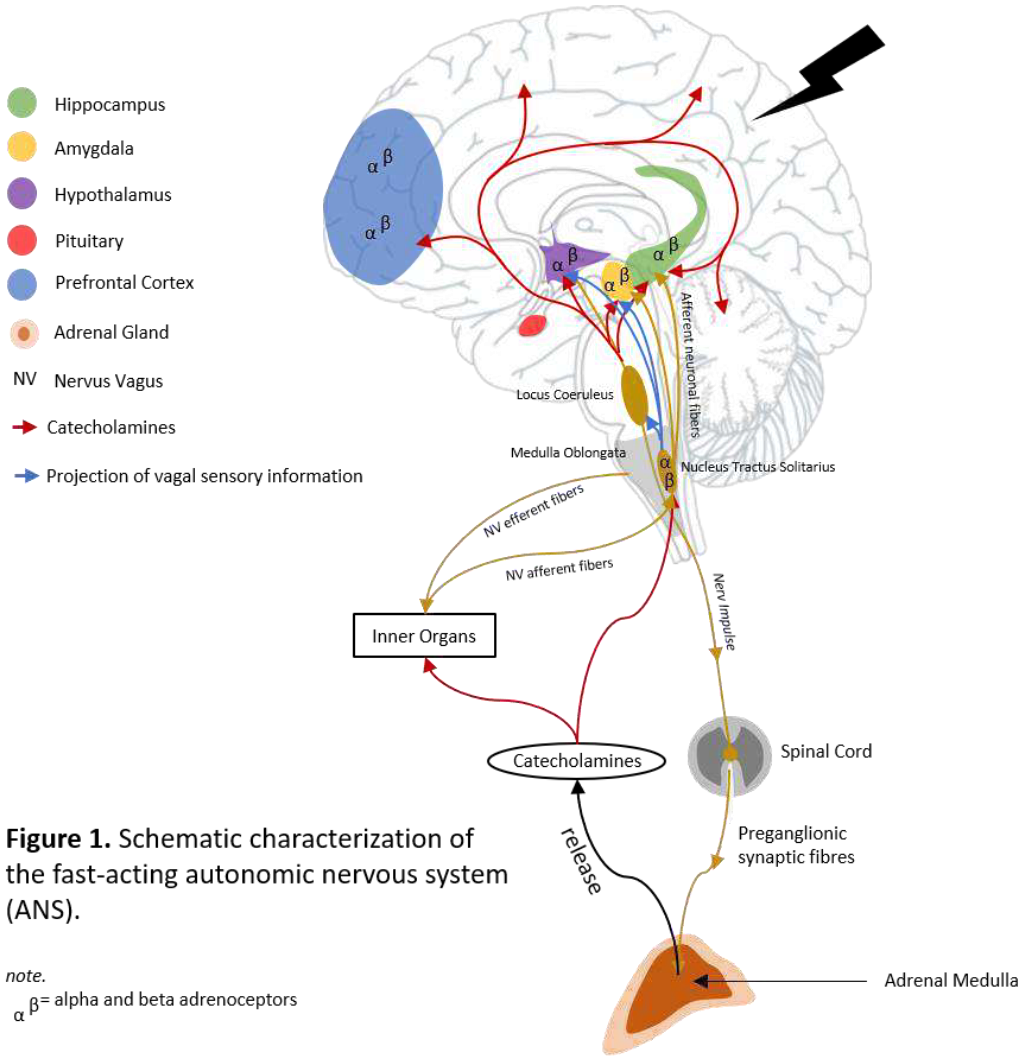

Figure 1. Schematic characterization of the fast-acting autonomic nervous system (ANS).

note.
α β= alpha and beta adrenoceptors

1.2.1.2. The hypothalamus-pituitary-adrenal (HPA) axis

Contrary to the ANS, the HPA axis acts via a hormonal cascade which explains the slower impact. When challenged with a stressor, the hypothalamus releases the corticotropin-releasing-hormone (CRH). The anterior pituitary responds with the secretion of the adrenocorticotropic hormone (ACTH), which in turn provokes the release of glucocorticoids, a subgroup of corticosteroid hormones, from the adrenal cortex (Schwabe & Wolf, 2013; Ulrich-Lai & Herman, 2009). Thus, hormone levels within the brain increase with a delay of approximately 20 minutes and take one to two hours to be normalized (Krugers et al., 2012). Glucocorticoids are known as cortisol in human

beings and corticosterone in most animals and are lipophilic, which enables cortisol to pass the blood brain barrier (De Kloet et al., 2005; Krugers et al., 2012). As a result, cortisol mobilizes energy resources through gluconeogenesis and by suppressing the immune-system (de Kloet, de Kloet, de Kloet, & de Kloet, 2019). Furthermore, the HPA axis prevents itself from overshooting and restores homeostasis via an efficient negative feedback-system whereby cortisol inhibits the secretion of CRH and ACTH from the paraventricular nucleus (PVN, a part of the hypothalamus) and the anterior pituitary (Gjerstad, Lightman, & Spiga, 2018). Furthermore, it modulates neuronal excitability in the amygdala, the hippocampus and the PFC, which in turn regulates the stress response (Hermans et al., 2014; Quaedflieg & Schwabe, 2018). On a molecular level, this feedback-system seems to be mediated by the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR), two receptors with different features in matters of cortisol response: The MR has a tenfold higher affinity to cortisol than the GR, which results in an almost constant occupation, even in non-stressful conditions. Within the brain, research shows that the MR's denseness is the highest in limbic structures like the amygdala and the hippocampus (especially in the CA3 subregion), which corresponds with the assumption that it plays a critical role in appraisal processes and ensuing required responses and decisions to novel situations (De Kloet, Meijer, de Nicola, de Rijk, & Joels, 2018; de Kloet, 2014). In contrast, the GR is only fully activated in periods of stress or during the so called "*cortisol awakening response"*, a circadian peak in cortisol release in the morning. Important areas with higher density of GR in the brain are the PVN, the hippocampus, the prefrontal cortex (PFC) and the limbic-system. Thus, GRs are more widely distributed and involved in behavioral adaptation, memory storage of new situations and recovery, but are also suggested to play a role in

altruistic behavior as a response to a stressor (De Kloet et al., 2018; de Kloet, 2014). For a schematic characterization of the HPA axis, see also figure 2.

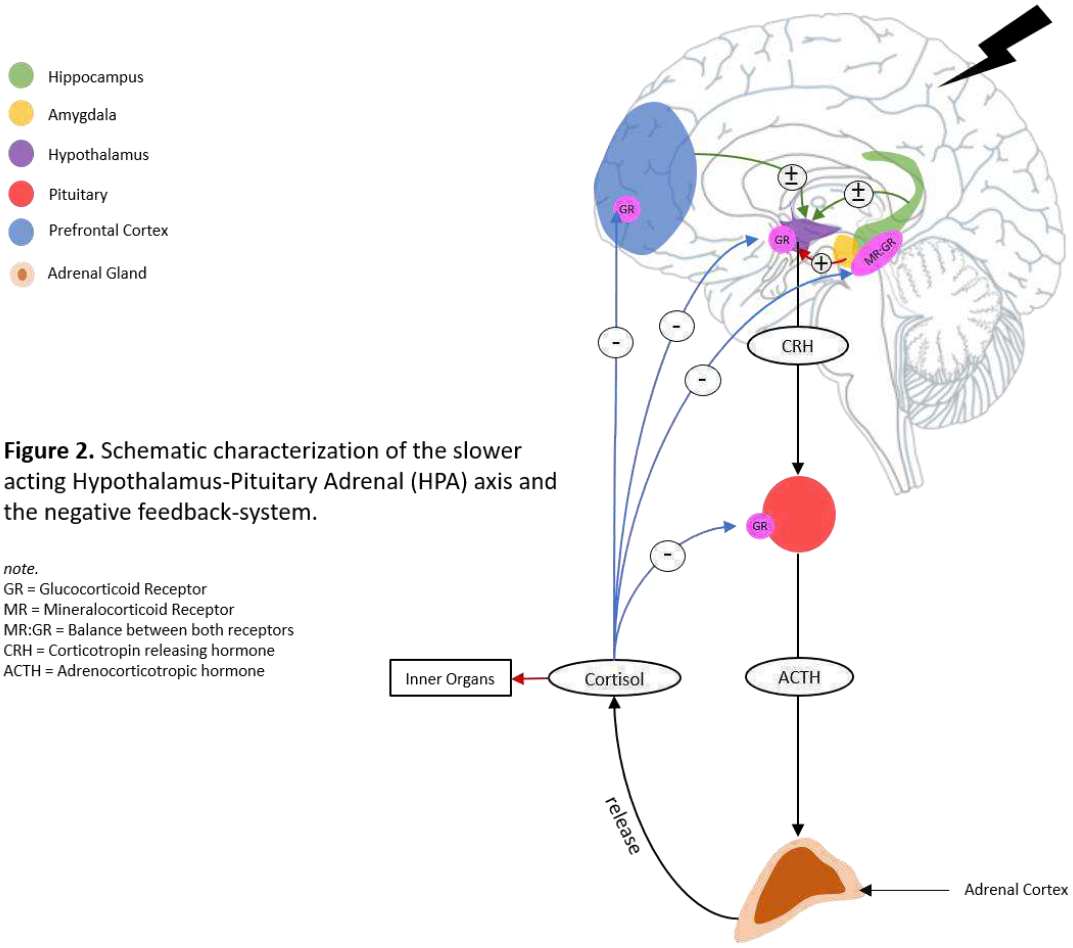

Figure 2. Schematic characterization of the slower acting Hypothalamus-Pituitary Adrenal (HPA) axis and the negative feedback-system.

note.
GR = Glucocorticoid Receptor
MR = Mineralocorticoid Receptor
MR:GR = Balance between both receptors
CRH = Corticotropin releasing hormone
ACTH = Adrenocorticotropic hormone

The involvement in different behavioral reactions to a stressor in both receptors point to another important finding: Besides the affinity and the distribution of MR and GR, recent research additionally postulates slow genomic and fast membrane-associated, non-genomic effects for both receptor types (de Kloet, Karst, & Joëls, 2008; Quaedflieg & Schwabe, 2018). In sum, these findings were merged in the *MR:GR balance hypothesis* (de Kloet, 2014; de Kloet et al., 2008; De Kloet, Vreugdenhil, Oitzl, & Joëls, 1998). The MR:GR balance hypothesis postulates that only a concerted interplay between the receptors in chronology and affinity enables a healthy adaptation to environmental demands. This concept of a hormonal balance can be widening since an effective and healthy stress reaction not only depends on the MR:GR balance but possibly on a well-orchestrated

interaction between the neurotransmitters and hormones of the HPA axis and the ANS (Krugers et al., 2012; Quaedflieg & Schwabe, 2018). Sections 1.2.1.1 and 1.2.1.2 illustrate that the stress hormones and neurotransmitters of both axes effect the PFC and the limbic structures at different time points due to fast and slower acting mechanisms. During and after acute stress the stress hormones only act in concert for a specific period of time (see also figure 3). Thus, changes in activation pattern or in the negative feedback-system are likely to result in a dysfunctional stress adaptation, which in turn might contribute to altered emotional and cognitive responses to stress in BPD. Therefore, the next sections provide an overview about current empirical evidence for alterations of the stress axes in BPD patients. Most cited studies were conducted with female patients. If available, for cited meta-analyses the percentage of female participants is specified. Studies which tested a mixed sample (male and female participants) are labeled in the text.

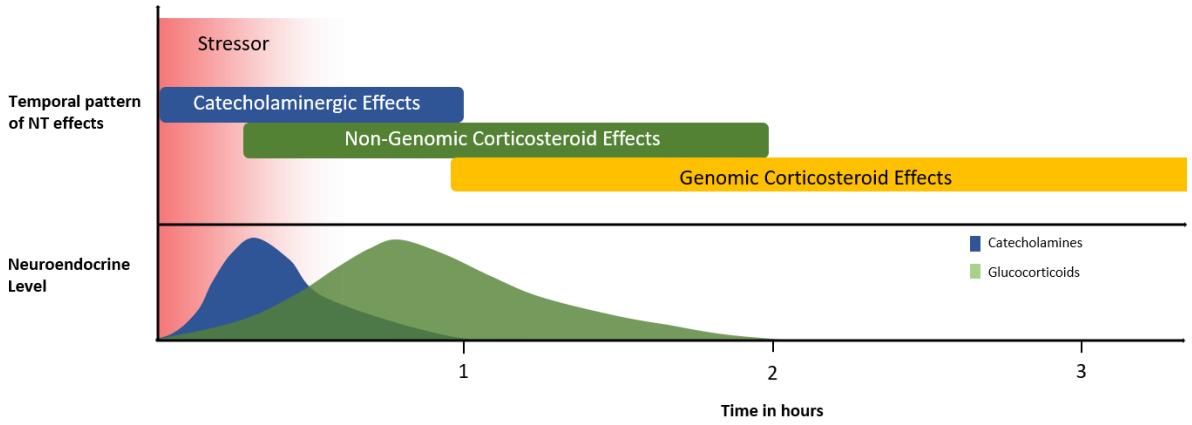

Figure 3. Schematic characterization of the development of catecholamine and glucocorticoid levels within the brain after acute stress. The upper area illustrates the effect time window of neurotransmitters on a cellular level. Adapted from Hermans, Henckens, Joëls, and Fernández (2014). *note.* NT = Neurotransmitter

1.2.1.3. Alterations of the ANS in BPD

Studies investigating chronic alteration of the ANS in BPD so far used several markers to assess possible dysfunctions: respiratory sinus arrhythmia (RSA), which reflects the balance

between the heartbeat and the respiratory rhythm and constitutes a useful agent for dysregulations of the vagal tone[1]. Furthermore, heart rate variability (HRV) is frequently assessed to identify differences between patients and healthy controls and is defined as the time interval between heartbeats. Low HRV and RSA account for decreased regulatory processes of the ANS (e.g. Porges, 2009; Sztajzel, 2004; van Ravenswaaij-Arts, Kollee, Hopman, Stoelinga, & van Geijn, 1993). Moreover, heart rate (HR) and skin conductance (SCR) are used at times to detect alterations of the autonomic nervous system (Ebner-Priemer et al., 2008; Ebner-Priemer et al., 2007; Eddie et al., 2018; Kuo & Linehan, 2009). In matters of baseline RSA, several studies, to date, postulated lower values for BPD patients as a marker for an elevated sympathetic activation in concert with a dampened parasympathetic vagal tone, compared to healthy controls (Kuo & Linehan, 2009; Thomson & Beauchaine, 2018; Weinberg, Klonsky, & Hajcak, 2009, mixed male and female BPD sample). These results are assisted by a growing body of evidence for decreased vagally mediated HRV in BPD (for a meta-analysis, see Koenig, Kemp, Feeling, Thayer, & Kaess, 2016). However, contrary findings exist, as e.g. Austin, Riniolo, and Porges (2007) only showed differences regarding RSA on trend level. Furthermore, Meyer et al. (2016) only revealed differences in matters of HRV for patients with a posttraumatic stress disorder (PTSD) and HCs, whereas female BPD patients did not show altered HRV values. Meyer et al. (2016) thereupon linked their finding of an altered HRV to CT/ACE, which is surprising in the light of the missing connection to BPD. A recent study by Eddie et al. (2018, mixed male and female BPD sample) measured a comprehensive set of ANS variables and found no differences regarding HRV in BPD patients compared to healthy controls. Interestingly, overall altered baseline results for HR became non-significant, when the authors added physical

[1] **Vagal Tone:** The vagal tone describes the active inhibition of the sympathetic nervous system by the vagal nerve. In a stressful situation this inhibition is rapidly reduced to quickly enable the sympathetic branch of the ANS to innervate the heart activity and mobilize energy (Balzarotti, Biassoni, Colombo, & Ciceri, 2017).

exercise as a covariate to their statistics. Thus, Eddie et al. (2018) concluded that an altered ANS in BPD might be, at least in part, also a lifestyle question.

When provoking an acute stress response in BPD patients, most studies used a well-established laboratory psychosocial stressor which simulates a job interview and reliable activates the HPA axis and the ANS (Kirschbaum, Pirke, & Hellhammer, 1993; for a detailed description see 2.2.5). Subsequently, heart rate (HR) or salivary alpha amylase[2] (sAA) as markers for sympathetic reactivity are measured. Interestingly, the majority of studies predominantly revealed a blunted sympathetic activation in female BPD patients compared to female HC as a response to psychosocial stress (Aleknaviciute et al., 2016 (HR); Deckers et al., 2015 (HR); Nater et al., 2010 (sAA); Scott et al., 2013 (sAA)). Confirming these results, Kaess, Parzer, Koenig, Resch, and Brunner (2016) also revealed a blunted HR in female BPD patients compared to HC after provoking stress with an aversive noise task. However, Inoue et al. (2015) conducted a study with a mixed male and female sample and did not find any differences between BPD patients and HC regarding the impact of psychosocial stress on alpha-amylase which is in line with the results by Simeon, Knutelska, Smith, Baker, and Hollander (2007) who also triggered an acute stress response in a mixed BPD sample, but detected plasma noradrenaline in blood samples as a marker for sympathetic activity and revealed no differences between groups. One study even reported higher sAA levels in female BPD patients compared to HC after acute stress (Ehrenthal, Levy, Scott, & Granger, 2018), which is in line with the findings by Kuras et al. (2017), who found increased sAA after psychosocial stress for a group with adverse experiences during childhood. Interestingly, Kuras et al. (2017) also tested a mixed sample of male and female participants.

[2] **Salivary Alpha Amylase (sAA):** sAA is a digestive enzyme which is synthesized in the saliva glands and stored in secretory granules (Granger, Kivlighan, El-Sheikh, Gordis, & Stroud, 2007). Research has shown that psychosocial stress increases the production of salivary alpha amylase by the interaction with the ANS. Therefore, it serves as a useful marker for ANS activation (e.g. Rohleder, Wolf, Maldonado, & Kirschbaum, 2006; van Stegeren, Rohleder, Everaerd, & Wolf, 2006).

Taken together, the results indicate a dysregulated basal ANS-system, however, results do not show a consistent direction as some studies revealed a clear elevated sympathetic activation in concert with a dampened parasympathetic vagal tone compared to HC, whereas other studies did not find differences between groups. In matters of acute stress, most studies using a well-established psychosocial stressor revealed a blunted sympathetic reaction across variables in female BPD patients compared to female HC. Again, results are not homogeneous as some studies revealed enhanced sympathetic reactivity or did not detect differences between groups, which is suggested to arise from the multifactorial complexity of the stress-system and varying outcome variables (Eddie et al., 2018).

1.2.1.4. Alterations of the HPA axis in BPD

Regarding chronic alterations of the HPA axis in BPD, studies so far are more consistent compared to the ANS. In sum, most of the existing studies show evidence for an increased basal cortisol release in concert with a reduction in sensitivity of the feedback-system (Wingenfeld, Spitzer, Rullkötter, & Löwe, 2010; Zimmerman & Choi-Kain, 2009). Recently, this assumption was confirmed by a quantitative meta-analysis. Drews et al. (2018) detected 37 studies and looked at several subgroups to identity differences between HC and BPD patients. Their sample overall comprised 83% females. In a first step, 29 studies out of 37 pictured single cortisol assessments and the authors did not find any differences between groups. Interestingly, a subgroup of five studies investigating continuous cortisol assessment were also compared. The BPD group constantly showed increased continuous cortisol levels in contrast to HC. Since single cortisol assessments are highly fluctuant, a comparison of continuous cortisol seems more robust. However, Thomas, Gurvich, Hudaib, Gavrilidis, and Kulkarni (2019) published a systematic review and summarized 12 studies reporting on basal cortisol levels in BPD patients. In contrast to Drews et al. (2018), they

concluded that BPD patients show a decreased basal cortisol level compared to healthy controls. It is worth mentioning that Thomas et al. (2019) did not separate for continuous and single assessment of cortisol and mixed several study protocols.

Furthermore, Rinne et al. (2002) were one of the first who explicitly tested the negative feedback-system of the HPA axis in female BPD patients with and without a history of CT/ACE. They used the combined dexamethasone/corticotropin releasing hormone (DEX/CRH)[3] test (Heuser, Yassouridis, & Holsboer, 1994) to actively challenge the HPA axis and it's negative feedback-system. The authors found that BPD patients who experienced CT/ACE did not suppress the released cortisol compared to BPD patients with non or a mild CT/ACE history. Interestingly, PTSD as a co-morbidity attenuated the response to the DEX/CRH test. This is in line with Wingenfeld, Hill, Adam, and Driessen (2007) who also used the DEX/CRH test and found less suppression in female BPD patients but only in those with low PTSD symptomatology, underlining the importance of co-morbidities. These data were confirmed by Carvalho Fernando et al. (2012). As in the study by Rinne et al. (2002), CT/ACE again was highly linked to an altered suppression and rather contributed to an explanation of the data than the BPD symptomatology itself. However, the results in this field are not univocal and contrary results exist, mostly depending on co-morbidities and/or CT/ACE (Carrasco et al., 2018, mixed male and female BPD sample; Grossman et al., 2003, mixed male and female BPD sample; Lange et al., 2005)

To not only investigate in chronic alterations, some studies used a psychosocial stressor to identify the acute physiological stress response in female BPD patients compared to female healthy controls and predominantly revealed a blunted cortisol release (Aleknaviciute et al., 2016; Deckers

[3] **DEX/CRH:** In the combined DEX/CRH test the release of ACTH from the pituitary is suppressed by an administration of dexamethasone (DEX). Subsequently, CRH is dispensed which in turn challenges the HPA axis. Thus, the degree of a suppressed cortisol release serves as a marker for the correct function of the HPA axis.

et al., 2015; Nater et al., 2010; Scott et al., 2013). These results are in line with Ehrenthal et al. (2018) who linked the blunted cortisol response after stress in their female BPD sample to attachment anxiety and CT/ACE. Furthermore, Kaess et al. (2012) investigated in female patients engaging in Nonsuicidal Self-Injury (NSSI), a behavior frequently seen in BPD patients, who again showed an attenuated cortisol response to stress. However, other studies using conflict-scenarios (Lyons-Ruth, Choi-Kain, Pechtel, Bertha, & Gunderson, 2011; Walter et al., 2008, mixed male and female BPD sample) or a cyberball-paradigm[4] (Jobst et al., 2016) did not reveal differences between groups in matters of cortisol. Interestingly, Inoue et al. (2015) conducted one of the few studies with a male and a female BPD patient subsample. They also used a psychosocial stressor and found a decrease in cortisol only in female BPD patients, whereas the male participants showed an elevated cortisol response. Finally, Drews et al. (2018) confirmed the depicted findings and integrated 10 studies in their meta-analysis, which used a psychosocial threatening situation to evoke a stress response. They found an overall blunted cortisol reaction in BPD compared to HC.

Taken together, the results for the HPA axis are more consistent than the data for ANS alterations as several studies and a comprehensive meta-analysis revealed an elevated basal cortisol secretion for female BPD patients compared to HC. Moreover, data suggest that BPD patients show a blunted HPA axis activation in response to an acute stressor.

In sum, the results indicate that BPD patients show a chronically elevated HPA axis in concert with a reduced negative feedback-system. Furthermore, studies revealed a blunted reaction of both stress axes to an acute psychosocial stressor. However, the results are not univocal and divergent findings exist, especially for the ANS. These varying data across studies might be due to several

[4] **Cyberball Paradigm:** The cyberball paradigm is an online ball-tossing game. Participants belief to play with other individuals. In reality, the "other participants" are controlled by the investigator. Due to various options of the researcher to regulate the game, variables like ostracism, prejudice or discrimination can be manipulated (Williams & Jarvis, 2006).

limitations in past research. First, the sample size of some studies so far was rather small (e.g. Nater et al., 2010; Simeon et al., 2007; Walter et al., 2008). Second, there is robust evidence that co-morbidities might play a crucial role in stress axes disturbances (Wingenfeld, Spitzer, Rullkötter, et al., 2010). Especially the posttraumatic stress disorder (PTSD) and the major depression (MD) were frequently linked to an altered stress response and are also highly common in BPD patients (Pagura et al., 2010; Wingenfeld et al., 2013; Zimmerman & Mattia, 1999). In matters of these co-morbidities, studies vary across their design, as some included BPD patients with a major depressive episode whereas others excluded these patients and often the status as lifetime or current diagnosis is lacking (Drews et al., 2018). For PTSD, Drews et al. (2018) further mentioned in their meta-analysis that more than a third of the existing studies did not report on PTSD and therefore a systematic evaluation of co-morbidities is missing. Finally, a comprehensive set of studies used a well-established psychosocial stressor to activate both stress axes and thus a full-blown stress response in their study samples. However, to date no study applied a placebo-condition to their investigation, and data about intraindividual reactions to a stress-situation compared to a placebo-condition in BPD patients are missing. The heterogeneity of study results in concert with the mentioned limitations lead to the first aim of this dissertation:

AIM I: The first aim of this dissertation is to further examine the HPA axis and ANS response in BPD patients to an acute psychosocial stressor and compare the reaction to a placebo-condition and to a matched group of healthy controls.

1.3. STRESS AND MEMORY

In the sections above it became obvious that the hormones and neurotransmitters of the HPA axis and the ANS not only manage an individual's stress reaction but are also able to directly pass

the blood brain barrier or indirectly impact on central neuronal networks which are relevant in terms of higher cognitive processes like the PFC, the hippocampus and the amygdala (e.g. De Kloet et al., 2005; Krugers et al., 2012; Wolf et al., 2016). Research over the last decades confirms that stress alters several cognitive domains, especially the memory-system in HC, and that a dynamic interplay and a correct sequencing of the released neurotransmitters and hormones is necessary for a successful reaction to a threatening situation (Quaedflieg & Schwabe, 2018; Schwabe, 2017; Schwabe & Wolf, 2013). Furthermore, this interaction of the stress axes might be disrupted in BPD patients which raises the question: Does acute psychosocial stress acts differently on cognitive domains in BPD patients compared to HC? The following chapters provide a short overview about the memory-system in general and current knowledge about the impact of acute stress and stress-hormones in healthy individuals and BPD patients.

1.3.1. The memory-system

Like the stress-system, memory formation and storage are dynamic processes, which on the one hand are highly effective and flexible, but on the other hand come at the cost of fragility, especially for recently encoded information (Quaedflieg & Schwabe, 2018). After encoding of new content, the consolidation process begins where memory traces become more stable over time and are connected to networks of previous stored experiences. However, these memory entities by far are not fixed domains and research shows that the recalling of already consolidated memories recreates convertibility depending on the context and exogenous and endogenous influences, like for instance a stressful situation (Quaedflieg & Schwabe, 2018; Schwabe, 2017; Schwabe & Wolf, 2013; Wolf, 2018). In a classic view of memory entities, declarative memory as a long-term storage represents *semantic memory*, which consists of factual information about the world and *episodic memory,* which contains information about personal experiences during the life-span (Tulving,

1972; Tulving & Markowitsch, 1998). It becomes obvious that episodic memory includes autobiographical information as a core feature, which is highly relevant for individuals to develop a sense of self and integrate experiences into their personal history (Pillemer, 2003). Besides a long-term storage to integrate new information in a context of life-span experiences or recall memories from the past, there is a necessity to immediately process activated memories and deal with flexible changing environmental demands. Hence, Baddeley and Hitch (1974) specified existing frameworks about working memory abilities and developed the "*multicomponent working memory*" model. This model is based on four separate systems, which ought to be interconnected: The *central executive* represents the main control unit, which organizes the three subsystems; the *phonological loop*, the *visuospatial sketchbook*, and the *episodic buffer*. These elements are designed to shortly store, and process activated information and guide further behavior or cognitive processes like decision making, goal directed behavior or attention. The following sections give an overview, how acute stress impacts on these different memory systems in healthy controls and BPD patients.

1.3.1.1. Impact of stress on memory in HC

During the last decades, research focuses on the impact of an acute psychosocial stressor or a pharmacological administration of a single stress hormone on encoding, consolidation or retrieval processes. In general, the main conclusion regarding the impact of acute stress on memory in healthy individuals suggests that stress differently impacts on consolidation of new information and its retrieval. The consolidation process is predominantly enhanced, whereas the retrieval is impaired across studies (e.g. de Quervain et al., 2009; Hidalgo, Pulopulos, & Salvador, 2019; Schwabe, 2017; Shields, Sazma, McCullough, & Yonelinas, 2017; Wolf, 2009). In line with the activated stress-system recent research suggests that the impact of stress on memory highly depends on the chronology of hormones within the brain and that a well-orchestrated interplay between the neurotransmitters

of the HPA axis and the ANS is crucial for a successful memory formation/adaptation under stress (Hermans et al., 2014; Krugers et al., 2012; Quaedflieg & Schwabe, 2018). In this dynamic model, the fast acting ANS activates the amygdala and enhances alertness and the attention towards a stressful situation via adrenaline and noradrenaline. The activation of the ANS shifts the mental processes from flexible executive control mechanisms to more habitual ones by enhancing the connectivity of a neuronal network, which is involved in processing of salient information (Schwabe, 2017; Schwabe & Wolf, 2013). This explains improved initial encoding processes in terms of acute stress (Quaedflieg & Schwabe, 2018). The salience network (SN) is organized around the already mentioned amygdala and also comprises the hypothalamus and the dorsal anterior cingulate cortex (dACC) (Schwabe, 2017). It is primarily involved in detecting salient external and internal stimuli. This corresponds well with findings indicating that emotional information is better encoded and consolidated according to stress than neutral stimuli (e.g. Wolf, 2009). Shortly after the catecholaminergic effects, rapid non-genomic MR effects on the one hand enhance the activating effect of the catecholamines and on the other hand increase the excitability in amygdala and hippocampus neurons (Hermans et al., 2014). Studies on brain tissue-samples additionally show that changes of the interplay between neurotransmitters result in absent or even diminished neuronal excitability (Krugers et al., 2012). Furthermore, the activity of the PFC is reduced during the first sequences of acute stress (Hermans et al., 2014), which underlines the shift to habitual processes and an impairment in executive functions, which fits well to data on impaired working memory and memory retrieval, since the consolidation of new memory is protected from external disturbances (Jiang & Rau, 2017; Qin, Hermans, van Marle, Luo, & Fernández, 2009; Roozendaal, McReynolds, & McGaugh, 2004; Wolf, 2009; Wolf, 2017). Interestingly, studies using a selective MR agonist, rather revealed enhancing effects on declarative and working memory compared to a placebo (e.g. Hinkelmann et al., 2015; Otte et al., 2014). The authors suggest that MR expression

also in the PFC might contribute to these results, which would mean that a missing initial impact of catecholamines on the PFC in concert with an MR agonist might enhance memory performance (Otte et al., 2014). Furthermore, one could suggest that rather mixed results on autobiographical memory (AM) arise due to different chronological intervals of remembered content (Shields et al., 2017). This suggestion is supported by Fleischer et al. (2017) who showed that the impact of cortisol depends on the remoteness of remembered AM in HC.

The rapid effects of acute stress support an orientation in the environment and fast, successful access to coping strategies. In the long run, genomic and non-genomic effects, predominantly driven by the GR, are suggested to reverse the effect on neuronal networks by enhancing PFC activation and diminishing amygdala activity (Hermans et al., 2014; Quaedflieg & Schwabe, 2018). Thus, it restores executive control functioning and suppresses the emotional and habitual related networks. This central executive network (CEN) seems to be activated in higher cognitive functions such as the control of attention and working memory. The CEN is mainly based around the PFC but also comprises of the posterior regions like the posterior parietal cortex (PPC) (Hermans et al., 2014; Joëls, Sarabdjitsingh, & Karst, 2012; Quaedflieg & Schwabe, 2018). This assumption is in line with Henckens, van Wingen, Joëls, and Fernández (2011) who conducted a fMRI study and dispensed 10mg hydrocortisone either 30 or 240 minutes prior to a working memory task. Working memory was enhanced by cortisol only after 240 minutes, together with increased neuronal activity in the dorsolateral PFC. No effects were found after 30 minutes, which underlines the slow genomic GR driven effects on the CEN.

In addition, studies revealed that this concerted interplay also depends on the dosage of released hormones and that an inverted U-shaped dose response model seems suitable for neuronal excitability and memory processing (Joëls, Fernandez, & Roozendaal, 2011; Wolf, 2017). Especially the excitability of amygdala neurons, which are suggested to predominantly modulate

the stress response, react sensitive to different amounts of released stress-hormones (Joëls, Karst, & Sarabdjitsingh, 2018; Roozendaal, Okuda, Van der Zee, & McGaugh, 2006). Moreover, this modulation might also be based on the unequal affinity of the MR and the GR to cortisol (Joëls, 2006).

The possible impact of stress hormones and neurotransmitters on brain site connectivity during a stressful situation is depicted in figure 4. It becomes obvious that an imbalance of the neurotransmitters, like in BPD patients, might result in altered memory dynamics.

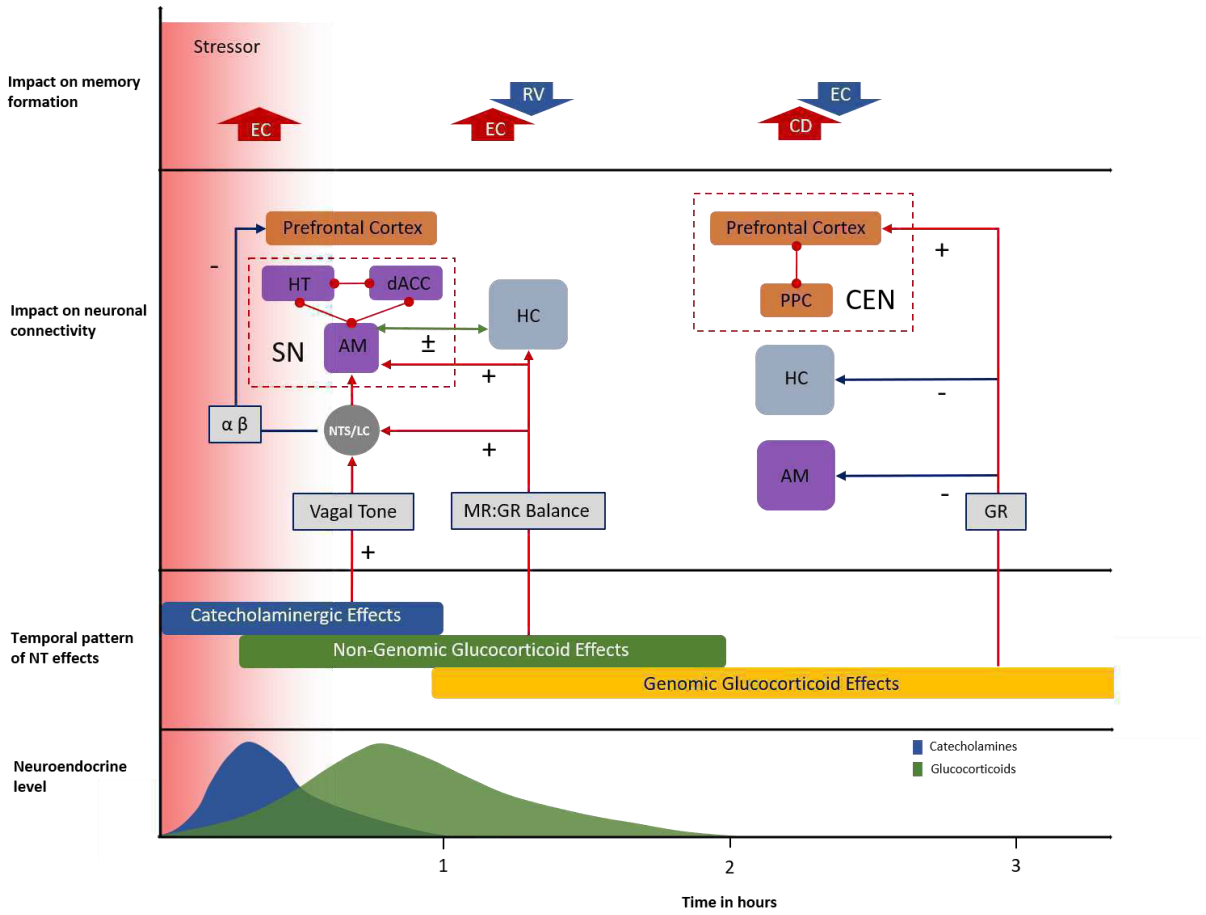

Figure 4. Schematic characterization of the interactional temporal pattern of catecholamines and glucocorticoids after acute stress and their impact on different receptors on the one hand and on neuronal network connectivity on the other hand. Furthermore, enhanced and diminished memory processes according to stress are depicted. Figure 4 is adapted and modified from Hermans et al. (2014); Schwabe (2017) & Quaedflieg and Schwabe (2018)

note. HT = Hypothalamus, dACC = dorsal anterior cingulate cortex, AM = amygdala, HC = Hippocampus, NTS/LC = nucleus tractus solitarius/locus coeruleus, PPC = posterior parietal cortex, GR = glucocorticoid receptor, MR = mineralocorticoid receptor, EC = encoding, RV = retrieval, CD = consolidation, SN = salience network, CEN = central executive network, α = alpha adrenoceptors, β = beta adrenoceptors, NT = Neurotransmitters

1.3.1.2. Impact of stress on memory in BPD

Research on the impact of psychosocial stress or single stress hormones on memory in BPD patients is scarce. In 2013, Wingenfeld et al. administered 10mg of synthetic cortisol (Hydrocortisone, for a detailed description, see section 2.2.5) to a group of female BPD patients and compared their performance in declarative, autobiographical and working memory to a group of healthy female controls. The BPD patients showed an increase in memory retrieval for all domains which was comparable to the level of non-stressed HC, whereas the stressed control group exhibited the expected pattern of an impaired retrieval, compared to placebo. Thus, a high add-on of cortisol seems to have rather enhancing effects on memory in BPD patients. Although hydrocortisone predominantly acts on the GR a small impact on MR cannot be ruled out (see sections 1.2.1 and 1.2.2). Therefore, Wingenfeld et al. (2015) tried to disentangle the receptor function and conducted a second study, where they dispensed 0.4 mg fludrocortisone, a selective MR agonist, to both groups (female). Results show that the retrieval of verbal and visuospatial memory was impaired in BPD patients, whereas working memory performance was enhanced. The authors argue that the MR:GR balance in the hippocampus in BPD patient might be disrupted. Therefore, hippocampus-based functions are impaired whereas prefrontal cortex dependent abilities seem to benefit from MR stimulation. In addition, Fleischer et al. (2015) found no impact of MR activation via fludrocortisone (MR agonist) on autobiographical memory in female BPD patients, which is also, at least in part, hippocampus-based. Furthermore, Kaess et al. (2016) explored differences in executive function between female BPD patients and HC using a single and dual-task paradigm. Stress was provoked through aversive noise versus no-noise as a control condition. Evoked stress led to an impaired performance in the dual-task, but the results were independent of group affiliation. Importantly, one could assume that in the study by Kaess et al. (2016) both stress-systems were activated, but the authors only reported on subjective stress and mean heart rate.

In sum, healthy controls predominantly show impaired semantic memory retrieval and working memory performance after acute psychosocial stress. Results for autobiographical memory are less univocal but impairing effects are also present. GR activation via synthetic cortisol (hydrocortisone) seem to result in the same effects as a psychosocial stressor. Single MR activation in turn enhances memory retrieval and working memory. Data for BPD patients are rare but remarkable, since GR stimulation led to enhanced memory performance in all tested domains, whereas fludrocortisone as a MR agonist had enhancing effects only on working memory, but impairing and absent effects on verbal, visuospatial and autobiographical memory. In addition, impairing effects for executive function were found by Kaess et al. (2016) who used aversive noise to provoke stress, however, the stress response was poorly validated. Figure 5 shows a summary about current knowledge about the impact of psychosocial stress and single stress hormones on memory in BPD patients and HC. Data on the impact of a well-validated psychosocial stressor on memory in BPD patients are missing in current research, which leads to the second aim of this dissertation:

AIM II: Since data on the impact of acute psychosocial stress are missing, the second aim of this dissertation is to confront a sample of female BPD patients and a sample of matched controls to a psychosocial stressor and a placebo-condition, respectively, in an intraindividual crossover design and subsequently assess the impact of the treatment on semantic and autobiographical memory retrieval and working memory performance.

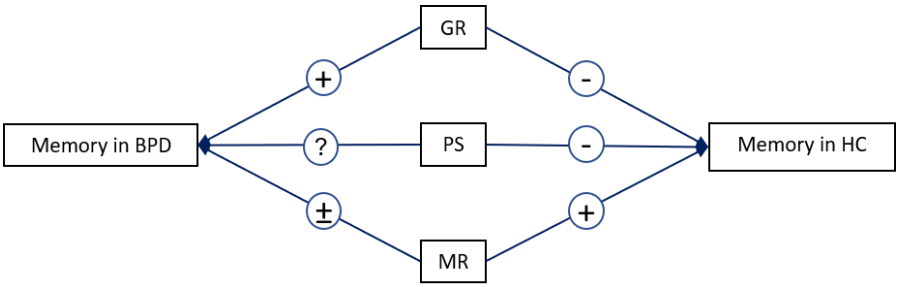

Figure 5. Summary of current evidence for the impact of stress and stress hormones on memory in female patients with a borderline personality disorder and healthy controls. This dissertation aims to answer the question if and how psychosocial stress (PS) impacts on memory in BPD?

note. PS = psychosocial stress, GR = glucocorticoid receptor, MR = mineralocorticoid receptor, BPD = borderline personality disorder, HC = healthy controls

1.4. STRESS AND SOCIAL COGNITION

Interpersonal skills are indispensable for an individual to successfully manage its social environment (Fiske & Taylor, 2013). BPD patients are known to suffer from disruptive relationships and vengeful disturbing social interactions. However, results in research are not univocal regarding the question, if BPD patients either suffer from impaired social skills or even show enhanced interactional abilities (Dinsdale & Crespi, 2013; Roepke et al., 2013). Since stress might be an important moderator in terms of social skills in BPD, the next section first provides an overview about the two important social cognitive variables in this dissertation (1.4.1). Section 1.4.1.1. further summarizes present empirical evidence about the impact of stress on social cognitive abilities in BPD. Since AIM IV in this dissertation focusses on the impact of a synthetic stress hormone on social cognitive abilities in HC, existing data on the impact of stress and stress hormones on social cognitive abilities in HC are provided in section 1.4.1.2.

1.4.1. Social cognition

Several cognitive and behavioral skills are necessary to successfully manage our social environment. Therefore, research comprises a wide variety of different outcome variables and measurements. *Social cognition* serves as an umbrella-term for all these variables and to integrate existing findings and concepts across studies (Allain, Togher, & Azouvi, 2019). However, comparing studies in this field becomes difficult at times since social cognition often refers to different abilities between investigations (Suchy & Holdnack, 2013). Therefore, the following subsection provides a short overview about the two important variables in the context of this dissertation:

a. *Empathy* refers to the ability of an individual to detect the mental state and share the emotion of its counterpart, which is crucial for the functioning of human relationships (Blair, 2005). A growing body of evidence suggests that empathy further comprises at least a *cognitive* and an *emotional* component (Gonzalez-Liencres, Shamay-Tsoory, & Brüne, 2013; Singer, 2006). According to Blair (2005), *cognitive empathy* determines the capacity of perspective-taking and subsequently deduce the mental state of another individual. *Emotional empathy*, in turn refers to an adequate emotional response, based on the observer's emotional perception of the counterpart's emotional state (Roepke et al., 2013).

b. Furthermore, *facial emotion recognition* seems to be a more basic concept in terms of social cognition. It refers to the ability to correctly recognize an expressed emotion in a counterpart's face, without interpreting or rather anticipating another person's intention or being aware of one's own emotional reaction (Barel & Cohen, 2018). Research on *facial emotion recognition* predominantly focuses on the ability to correctly identify a full-blown emotion (100%) on the one hand or to detect an emotion which is not fully expressed and thus more subtle in its expression (e.g. 40 %) (De Panfilis et al., 2018). Roepke et al. (2013) suggest that *facial emotion*

recognition can be seen as an integrative part of cognitive empathy, since it depicts a necessary background to correctly tune into a counterpart's mental state.

Thus, on the one hand social cognition merges a plurality of concepts, which are all highly interrelated and vary in complexity and on the other hand, testing emotional and cognitive empathy and facial emotion recognition seems to cover an extensive part of social cognitive abilities (Roepke et al., 2013).

1.4.1.1. Impact of stress on social cognition in BPD

Studies about social cognitive abilities in BPD patients so far revealed heterogenous results as some detected impaired social cognitive skills in BPD patients, whereas others did not find any differences or even an enhanced performance, compared to HC (Dinsdale & Crespi, 2013; Lazarus, Cheavens, Festa, & Rosenthal, 2014; Roepke et al., 2013). Besides other factors like co-morbidities (Roepke et al., 2013) or dysfunctional emotion regulation (Kalpakci, Vanwoerden, Elhai, & Sharp, 2016), the perceived stress during the task might play a critical role in observed differences between studies (Jeung & Herpertz, 2014; Lazarus, Cheavens, Festa, & Rosenthal, 2014). In total, only two studies so far explicitly investigated the impact of stress on social cognition in BPD patients (both female samples). Wingenfeld et al. (2014) administered fludrocortisone, as an MR agonist, to BPD patients and tested cognitive and emotional empathy by using a well validated empathy test, namely the multifaceted empathy task (MET), for a detailed description, see 2.2.6. MR stimulation enhanced emotional empathy in BPD patients but had no effect on cognitive empathy. Furthermore, Deckers et al. (2015) evoked stress in their female sample by using a psychosocial stressor and conducted a facial emotion recognition task. The test comprised of short video clips showing faces, which morphed from neutral to emotional. Interestingly, the authors found an increased performance in facial emotion recognition after stress for the BPD group and the healthy controls.

However, they stated that the task did not include a control-condition and the results cannot be separated from practice effects.

In sum, data about the impact of stress and stress-hormones on social cognition in BPD patients are scarce but show that it seems promising to separately detect cognitive and emotional empathy. MR stimulation enhances emotional empathy but has no impact on cognitive empathy in female BPD patients. Furthermore, a full-blown stress response seems to enhance emotion recognition in female BPD patients. The third aim of this dissertation focuses on missing data regarding the impact of a full-blown stress response, provoked by a psychosocial stressor, on empathy in BPD:

AIM III: The third aim of this dissertation is again to face a sample of female BPD patients and a sample of matched controls to a psychosocial stressor and a control condition, respectively, and subsequently assess their impact on cognitive and emotional empathy.

1.4.1.2. Impact of stress on social cognition in HC

Studies on the impact of stress on cognitive and emotional empathy in healthy controls vary in matters of stressor type and task. Wolf et al. (2015) used a well-established psychosocial stressor (for a detailed description, see 2.2.5) and tested cognitive and emotional empathy in healthy men. Participants showed an increase in emotional empathy after stress, but no effect emerged for cognitive empathy. Furthermore, Wingenfeld et al. (2014) stimulated the MR via a pharmacological approach in a sample of healthy females and again revealed no effect on cognitive empathy, but an enhancing impact on emotional empathy. These results are in line with a study by von Dawans, Fischbacher, Kirschbaum, Fehr, and Heinrichs (2012) who used a psychosocial stressor and revealed

an increase of prosocial behavior (trust, trustworthiness, and sharing) as a social cognitive ability in male participants. Tomova, von Dawans, Heinrichs, Silani, and Lamm (2014) also tested prosocial behavior after acute psychosocial stress but found an increase only in their female subsample. Male participants showed the opposite pattern. Interestingly, a recent study (fMRI) by the same group, however, showed enhanced prosocial behavior under acute stress in their male participants (Tomova, Saxe, Klöbl, Lanzenberger, & Lamm, 2019). Furthermore, in 2017 they pointed out that acute stress might lead to enhanced prosocial behavior, but this depends on contextual conditions and even decreasing effects might occur (Tomova et al., 2017).

According to facial emotion recognition, Deckers et al. (2015) found an increased performance after psychosocial stress in female HC. This is in line with Barel and Cohen (2018), who also revealed elevated facial emotion recognition after acute psychosocial stress. However, they also pointed out that this effects partly depends on the valence of the emotional expression. A recent study by Domes and Zimmer (2019) confirmed the previous findings and also revealed enhanced facial emotion recognition after acute psychosocial stress, independent of valence. Furthermore, Schultebraucks et al. (2016) selectively stimulated the MR but did not find any effects on facial emotion recognition.

Furthermore, some studies showed that sex might mediate the impact of stress on empathy (Smeets, Dziobek, & Wolf, 2009; Tomova et al., 2014). Smeets et al. (2009) found that the performance in a social cognition task was sex-specific and was mediated by the level of the cortisol response after psychosocial stress. Men with a higher cortisol level exhibited elevated scores for empathy, compared to men with lower cortisol. Women, in turn showed higher empathy scores in concert with lower cortisol levels. In addition, Gonzalez-Liencres, Breidenstein, Wolf, and Brüne (2016) could show that men and women under stress may even use different neuronal networks to process empathy.

In sum, psychosocial stress seems to enhance facial emotion recognition, whereas activation of the MR alone did not alter the participants performance. For empathy, studies revealed enhanced emotional empathy after experiencing psychosocial stress, which also refers to the stimulation of the MR alone. However, cognitive empathy seems not to be affected by psychosocial stress or MR stimulation. Furthermore, sex is suggested to be an important mediator for the impact of stress on empathy. Moreover, prosocial behavior was also enhanced by stress across studies, but seems to be more context and sex dependent. It becomes obvious that studies about the impact of single GR stimulation via synthetic cortisol are missing but necessary to disentangle receptor influence on social cognition, which leads to the fourth aim of this dissertation:

AIM IV: The fourth aim of this dissertation project is to dispense a single dose of synthetic cortisol to a balanced group of healthy male and female individuals and compare their performance in emotional and cognitive empathy and facial emotion recognition to another group receiving a placebo.

2. RATIONALE OF THE DISSERTATION PROJECT

The main aims of this dissertation are to gain further insight into the acute stress response in BPD patients and HC and subsequently test the impact of psychosocial stress on memory performance and empathy. Furthermore, the fourth aim focuses on the impact of a single stress hormone on empathy and facial emotion recognition and a possible moderating role of sex in HC. As outlined above, these aspects all resemble critical research gaps.

Regarding the empirical and theoretical background in section 1, the first study of this project examines if the female BPD patients' physiological stress axes show altered reactions to a naturalistic psychosocial stressor in comparison to a well-established control condition and to healthy controls (AIM I). Study one further addresses AIM II by providing results about the impact of the provoked stress response and the placebo-condition on the memory-systems in BPD and HC. Moreover, study two comprises the same BPD and HC sample as study one but illustrates the acute stress impact on empathy in both groups and compared to a placebo-condition. Finally, the impact of a single dose of synthetic cortisol on social cognition in healthy individuals will be explored in study three, by recruiting a balanced sample of healthy males and females to address AIM IV.

2.1. RESEARCH QUESTIONS AND HYPOTHESES

In this section, the crystalized research questions of each study are illustrated together with the corresponding hypothesis. In addition, the rationale of the three studies will be depicted to provide an overview on how the hypotheses were tested (section 2.2).

2.1.1. AIM I – BPD and physiological stress (Study I)

As section 1.1 indicates, there is considerable evidence that female BPD patients suffer from an altered stress-system, especially in response to an acute stressor (e.g. Drews et al., 2018; Weinberg et al., 2009). Although studies predominantly show an alteration, it remains unclear, if the stress response is increased or blunted or if there is even no difference to healthy controls. Furthermore, there is so far no study which implemented a placebo-condition in their design to compare the BPD patients' stress reaction. Due to these inconsistencies across studies and the lack of a placebo-condition in other studies, the following research question was formulated:

Research question:

Q-I: How does an acute psychosocial stressor influences the physiological stress-system in female BPD patients, compared to a placebo-condition and compared to female healthy controls?

Hypothesis:

Since most of the existing studies revealed a blunted physiological reaction to an acute psychosocial stressor and in addition the meta-analysis by Drews et al. (2018) points in the same direction, at least for HPA axis activation, we hypothesized that our female BPD sample will exhibit a blunted HPA axis and ANS reaction to a psychosocial stressor, compared to female healthy controls. Furthermore, we expected no differences between both groups in terms of the placebo-condition.

2.1.2. AIM II – BPD impact of psychosocial stress on memory (Study I)

As outlined above, there is compelling evidence for an altered stress-system in BPD (Drews et al., 2018). In addition, research in healthy individuals shows that stress impacts on memory specific neuronal networks and subsequently on memory formation processes (Quaedflieg & Schwabe,

2018). Research on the impact of stress on memory in female BPD patients so far is based on two studies using pharmacological approaches. They revealed diverse and partly contrasting results, compared to HC, which underlines the necessity of further research in this area (Wingenfeld et al., 2013; Wingenfeld et al., 2015). Furthermore, up to now, no study used a psychosocial laboratory stressor and a placebo-condition to investigate the impact of stress on memory in female BPD patients. Based on these assumptions, the following research question was formulated.

Research question:

Q-II: How does psychosocial stress impact on the memory performance in female patients with a borderline personality disorder compared to a placebo-condition and compared to female healthy controls?

Hypothesis:

Since there is no existing evidence for the impact of psychosocial stress on memory in female BPD our hypothesis was predicated on the interesting findings by Wingenfeld et al. (2013) who used a single administration of cortisol. In accordance with Wingenfeld et al. (2013) as the closest study in terms of design, we hypothesized that female BPD patients will show an increased declarative memory retrieval and working memory performance after psychosocial stress, compared to the placebo-condition, whereas the female HC will exhibit the expected decrease after stress, compared to the placebo-condition.

2.1.3. AIM III – Impact of psychosocial stress on empathy in BPD (Study II)

Research about interactional abilities in BPD patients are heterogeneous as some studies so far revealed enhanced, whereas others showed impaired interactional skills in BPD (Dinsdale & Crespi, 2013; Roepke et al., 2013). Stress is often associated with dysfunctional social interactions in BPD and therefore might serve as a moderator and in turn could explain, at least in part,

differences between studies regarding social cognitive abilities in BPD patients (Jeung & Herpertz, 2014; Lazarus, Cheavens, Festa, & Rosenthal, 2014). However, data on the impact of acute stress on social cognition, and more specific on empathy in BPD are rare. To date only one study, which used pharmacological MR stimulation is available. The authors showed an increase of emotional empathy in female BPD patients, but no effect on cognitive empathy (Wingenfeld et al., 2014). In addition, psychosocial stress seems to have an impact on social cognition performance in healthy controls (e.g. Wolf et al., 2015), but again data in this field are rare. Thus, the question arises if and how a psychosocial stressor impacts on empathy in female BPD and HC.

Research question:

Q-III: How does psychosocial stress affect empathy in female patients with a borderline personality disorder compared to a placebo-condition and compared to female healthy controls?

Hypothesis:

To date, results on the impact of stress on empathy in female BPD patients only derive from pharmacological MR stimulation, which enhanced emotional empathy. However, a psychosocial stressor provokes a full-blown stress response and therefore an activation of the ANS and the HPA axis. Psychosocial stress further challenges MR and GR receptors throughout the brain. Thus, we hypothesized that this full-blown stress response diminishes cognitive and emotional empathy in female BPD patients, compared to a placebo-condition. According to literature, for female HC we expect that psychosocial stress only enhances emotional empathy compared to a placebo-condition, whereas cognitive empathy is not affected by acute psychosocial stress.

2.1.4. AIM IV – Synthetic cortisol and social cognition in HC (Study III)

There is evidence that psychosocial stress enhances facial emotion recognition performance in healthy individuals (Deckers et al., 2015). However, single activation of the MR seems to have no

impact on facial emotion recognition (Schultebraucks et al., 2016). In matters of empathy, data are more complex as sex effects and cortisol levels are suggested to moderate the psychosocial stress impact (Smeets et al., 2009). Interestingly, there are no data on the impact of single GR activation on social cognition in healthy individuals due to a pharmacological approach. To allow for this gap in existing research the following research question was formulated.

Research question:

Q-IV: Does pharmacologically administered cortisol modulate facial emotion recognition and empathy in healthy young men and women?

Hypothesis:

Deckers et al. (2015) found increased facial emotion recognition in female HC after psychosocial stress. In line with these results, we expected an increase in emotion recognition performance after intake of synthetic cortisol compared to a placebo, independent of sex. For empathy and in line with Smeets et al. (2009), we based our hypothesis on high cortisol responders after a psychosocial stressor as a proxy for exogenous cortisol administration. We hypothesized an increase in cognitive and emotional empathy performance for men after hydrocortisone. Women in turn were expected to show an impairment in cognitive and emotional empathy after intake of synthetic cortisol.

2.2. DESIGN OF THE THREE STUDIES

In the next sections the design of the three studies will be outlined to link the information from section one to the derived research questions in section 2.1. All three studies were conducted in the Department of Psychiatry and Psychotherapy of the Charité - Universitätsmedizin Berlin, Campus Benjamin Franklin. Study I and II were approved by the ethics committee of the Charité -

Universitätsmedizin Berlin. Study III was approved by the national ethic committee of the German Psychology Association (DGPs). All participants provided their written informed consent.

2.2.1. Design of the studies

Study I is cross-over designed, and all participants experienced the psychosocial stress test and a placebo-condition (see section 2.2.5), respectively. Depending on the randomization process, half of the participants first received the stress-test and subsequently the placebo-condition, whereas the other half started with the placebo-condition. The delay between the two sessions (stress-test and placebo-condition) was at least seven days. Furthermore, study two comprises the same BPD and HC sample. However, study II has to be treated as a between-subject design, since the empathy test was only conducted at the first appointment. Finally, study III is a classic between-subject design, as half of the participants received hydrocortisone and the other half a placebo. The following sections provide a detailed description about recruitment, randomization and material of the three studies.

2.2.2. Participants recruitment

Study I and II

Although the ratio of BPD in the general population seems not to differ between men and women, the ratio of the clinical population is about 3:1 in favor of female patients (Chapman et al., 2019). It is suggested that female BPD patients are more likely to seek help and in turn appear more often in the medical care-system. Like the majority of studies in this field, due to practical reasons and to test a homogeneous sample, we only recruited female participants for study I and II. Furthermore, all participant in study I and II were between 18 and 55 years old and needed to have a body mass index (BMI) between 17.5 and 30 since extreme weights are known to impact the stress

axes (e.g. Stalder et al., 2012; Wirtz, Ehlert, Emini, & Suter, 2008). Female patients with a BPD on the one hand were recruited as inpatients from a special unit for the treatment of PTSD and personality disorders at the Campus Benjamin Franklin of the Charité – Universitätsmedizin, Berlin, Germany. On the other hand, female BPD outpatients and an age-based, oral contraceptives, free-cycling and education-matched sample of female healthy individuals was recruited via announcements on websites and public spaces. All outpatients and healthy individuals received an expense allowance of 100 Euros.

In study one and two the german version of the structured clinical interviews for DSM-IV (SCID-I and SCID-II) were conducted (Wittchen, Zaudig, & Fydrich, 1997). The SCID I provides information about an acute or lifetime axis I diagnosis which includes a major depression, other affective disorders and a posttraumatic stress disorder (First, Spitzer, Gibbon, & Williams, 1997). Wingenfeld et al. (2013) showed that an acute major depression diminished the enhancing effect of cortisol on memory in female BPD patients for which reason an acute major depressive episode led to exclusion from the investigation (for a detailed description of all exclusion criteria, see the respective study). To control for the impact of PTSD, half of the BPD patients were recruited with a co-morbid PTSD and the other half without a co-morbid PTSD. Furthermore, the SCID-II as a diagnostical instrument for personality disorders was primarily used to validate the BPD diagnosis and to detect additional co-morbid personality disorders (First, Gibbon, Spitzer, Williams, & Benjamin, 1997). In female healthy individuals a former or acute axis one or axis two (personality disorder) diagnosis led to exclusion from the investigation. Furthermore, all participants in study one and two filled out the short version of the borderline symptom list (BSL-23) (Bohus et al., 2009), the childhood trauma questionnaire (CTQ) (Wingenfeld, Spitzer, Mensebach, et al., 2010) and the Beck Depression inventory II (BDI-II) (Beck, Steer, & Brown, 1996) as self-report questionnaires to further detect

borderline symptomatology, experienced CT/ACE and depressive symptoms (for a detailed description of the questionnaires, see the respective study).

Study III

There is evidence that psychosocial stress differently affects social cognition in men and women (Smeets et al., 2009). Since Smeets et al. (2009) also found different effects of high and low cortisol responders contingent on sex, we recruited a balanced male and female sample of healthy young students via announcements on websites and at universities. To account for the impact of OCs or menstrual cycle (Merz & Wolf, 2017), female participants were either tested during the luteal phase or while taking oral contraceptives. Besides other exclusion criteria (for a detailed description, see Study III) axis one mental disorders were assessed using the SCID-I Screening Questionnaire. Acute or former mental disorders led to exclusion from the investigation. All participants received 20 Euros as expense allowance.

2.2.3. Randomization process

In study I the randomization followed a previously excogitated process since the cross-over design and paralleled versions of the memory tasks determined the procedure. In a first step, two sequences were designed. One sequence began with the psychosocial stressor, namely the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993, see section 2.2.5 for a detailed description) and participants experienced the placebo-condition at the second appointment. The other sequence was designed the other way around and started with the placebo-condition. Furthermore, the paralleled versions of a word list paradigm (A and B) (Terfehr et al., 2011a) and an adapted version of the autobiographical memory test (AMT) (Buss, Wolf, Witt, & Hellhammer, 2004; Schlosser et al., 2010; Williams & Broadbent, 1986) (A and B) were counterbalanced between the two treatment sequences (TSST vs. placebo-condition). Thus, four versions of the whole process were conceived,

and the participants were subsequently allocated to these sequences (figure 6). Since there is no paralleled version for the working memory task (WST) (Terfehr et al., 2011b), all participant conducted the same test after both conditions, however, the order of the neutral and negative trial varied across the TSST and the placebo-condition. The healthy controls experienced the same routine as their matched BPD patient counterpart.

	Test day 1	Test day 2
Version 1	TSST & A	PC & B
Version 2	TSST & B	PC & A
Version 3	PC & A	TSST & B
Version 4	PC & B	TSST & A

Figure 6. Schematic characterization of the randomization process in study I. If a participant, for instance, was allocated to Version 1, she experienced the TSST at the first appointment and the placebo-condition at the second appointment. The delay between test day one and test day two was at least seven days.

note. TSST = Trier Social Stress Test, PC = placebo-condition

Study II comprises the same BPD and HC sample as study I. Thus, the same randomization of the participants to the TSST and placebo-condition as in study I took place. To detect empathy, the Multifaceted Empathy Task (MET) (Dziobek et al., 2008) was conducted by all participants, but only at the first appointment after treatment (for a detailed description, see 2.2.6). Thus, half of the participants underwent the MET after the TSST, whereas the other half experienced the placebo-condition prior to the empathy task. Hence, study II has to be treated as a between-subject design.

In study III a computer-based randomization list was created on which basis all participants were allocated to hydrocortisone or placebo in a between-subject design.

2.2.4. Blinding

The first and the second study were single-blinded and placebo-controlled as the participants did not know in advance if they will experience the TSST or the placebo-condition at the first appointment. Due to the necessity for the examiner to guide the participants through the whole testing sequence and prepare and conduct the placebo-condition, study I and II could not be performed double-blinded. The third study was double-blinded, and placebo-controlled as neither the investigator nor the participants knew which testing condition the participants were allocated to.

2.2.5. Treatment selection

In order to provoke a full-blown stress response in the BPD patients and the HC in study I and II the Trier Social Stress Test (TSST) was conducted (Kirschbaum et al., 1993). The TSST is a well-established psychosocial laboratory stressor comprising a five-minute free speech and a five-minute lasting mental arithmetic task in front of a panel of judges. The TSST begins with a five-minute preparation phase in which the participants are asked to prepare the free speech with a focus on the question “why would you be a good candidate for your ideal job”. After the preparation phase the judges (one male and one female) enter the room and invite the participant to stand in front of the panel and deliver their talk, whereas they are not allowed to use previously prepared written material. Subsequently, the arithmetic task is conducted, which comprises a complex subtraction task and is primarily monitored by the judge of the opposite sex (in our studies the male judge). During the whole procedure, the judges wear white lab coats and are not allowed to provide verbal or non-verbal feedback to the participant. Furthermore, they monitor the participants’ performance in a written form and are trained to maintain a neutral facial expression. Finally, an audio and video recording equipment further simulate evaluation of the session. According to Dickerson and

Kemeny (2004) a situation is experienced as stressful, when it is socially evaluated and unpredictable, which fits very well to the TSST.

All participants consecutively experienced the TSST and a placebo-condition, which comprises the same chronology and routine as the TSST but without the socially evaluative and unpredictable elements. Thus, there are no judges and no audio / video equipment to evaluate the participants performance. Further, the free speech includes a topic which represents a positive situation and is chosen by the participants (e.g. the last holiday). Finally, the arithmetic test comprises a simple addition task (Het, Rohleder, Schoofs, Kirschbaum, & Wolf, 2009). Het et al. (2009) showed that this "Placebo-TSST" does not activate a physiological stress response but is comparable to the temporal routine and with regard to content of the stressful version of the TSST.

In study III a synthetic version of the endogenous glucocorticoid cortisol was administered to increase the participants cortisol levels. We used 10mg of hydrocortisone (Galen®) and an identical looking placebo. Hydrocortisone predominantly binds to the GR and acts as a receptor agonist; thus, it increases the activity of the receptor. Furthermore, hydrocortisone is metabolized within the body and reaches peak concentration approximately one to two hours after administration. According to Toothaker et al. (1982) its elimination half-life is between 1.3 and 1.6 hours.

2.2.6. Assessment of memory and social cognition

This section provides a short overview about the used memory and social cognition tasks across all studies. A detailed description of the tasks is available in the particular study.

Memory

To asses memory performance in study I, we used three different paradigms to cover a wide variety of memory-systems. Furthermore, to preserve comparability between studies, we used the same memory tasks as in Wingenfeld et al. (2013). First, a delayed word list paradigm was applied were the participants learned a list of 21 words in a five-trial setting. 24 hours later and after the treatment (TSST or placebo-condition, respectively), they were asked to freely recall as much words as possible (Terfehr et al., 2011a). Autobiographical memory was assessed via an adapted version of the autobiographical memory test (AMT) by Williams and Broadbent (1986) (Buss et al., 2004; Schlosser et al., 2010). In this test, participants are asked to remember and recall events from their biography. Therefore, the investigator subsequently presented six adjectives to the participants, which were written on cards. Finally, working memory was assessed by the use of a word suppression test (WST) (Terfehr et al., 2011b). The participants listened to audio sequences of alternating digits and interference words and were instructed to ignore the words and remember the correct sequence of the digits. Number of digits and words increased during the task. A detailed description of the memory tasks and the procedure is provided in study I.

Social cognition

In study II and III we used the Multifaceted Empathy Test (MET) (Dziobek et al., 2008) to detect emotional and cognitive empathy in all participants after treatment. The MET shows pictures of people in emotionally challenged moments on a computer-screen. The participants are instructed to answer two questions via the keyboard. The first question is “What is the person on the picture feeling” and assesses cognitive empathy. The participants have to choose the correct answer from a list of four. Emotional empathy is assessed via the question “How much are you feeling for the person”. Participants rate their emotional involvement on a Likert-scale (0= not at all, 9=very much).

Furthermore, in study III we additionally assessed facial emotion recognition abilities in healthy young individuals. The test comprised six male and six female faces from the NIMSTIM scale (Tottenham et al., 2009) which showed either a sad or an angry expression. The full emotion of 100 percent was reduced to receive two different intensities of every picture (40% and 80%). Besides the 100% and the two diminished intensities, neutral faces (0%) were used as a control condition. All pictures were shown on a computer-screen in randomized order and were rated by the participants via the keyboard.

2.2.7. Measurement of physiological data

For the assessment of salivary cortisol and alpha-amylase, Salivette® collection devices (Blue Cap®, Sarstedt, Germany) were used. In Study I and II overall six samples were collected for each individual and each test-day to monitor the cortisol and alpha-amylase level at baseline and after the psychosocial stress and the placebo-condition, respectively, until the end of the investigation. Since endogenous cortisol not only peaks in stressful situations but also due to a natural awakening response in the morning, hormone levels underly a circadian rhythm. Therefore, study I and II were conducted between 4:00 and 8:00 pm.

In Study III participants arrived at 1:00 pm and received either 10mg hydrocortisone or an identical looking placebo. The social cognition tasks started 45 minutes after intake of the tablet to watch for the cortisol to reach the brain. Saliva was collected directly prior to cortisol or placebo administration, respectively, and three times during the investigation to be able to illustrate the progress of the cortisol's increase and downregulation.

The saliva collection during the examination took place at room temperature. Directly after the experiment, the samples were frozen and stored at -80°C until biochemical analysis. Cortisol and alpha-amylase analysis were conducted in the Neurobiological Laboratory of the Department of

Psychiatry, Charité - Universitätsmedizin Berlin, Campus Benjamin Franklin. A detailed description of the cortisol and alpha-amylase analysis can be found in Duesenberg et al. (2016, cortisol) and Rombold et al. (2016, alpha-amylase). For free cortisol, the limit of detection was 0.2 nano Mol (nM), the intra-assay coefficients of variation were below 8% and below 10% for the inter-assay coefficients of variation. Intra- and inter-assay coefficients for alpha-amylase were both lower than 10%. For all samples and standards two copies were analyzed.

In studies I and II systolic and diastolic blood pressure were parallelly conducted to the salivary samples. An automatic device (Carescape 169 V100, GE Healthcare) was used and participants were instructed to not move during measurement.

2.2.8. Selection of the psychological tests

The TSST does not only provoke a physiological stress response but typically also alters subjective mood and arousal in participants. Thus, as a treatment check for subjective stress in study I and II, we applied the Multidimensional Mood Questionnaire (MDMQ) (Steyer, Schwenkmezger, Notz, & Eid, 1997), which measures three dimensions: good vs. bad, calm vs. nervous and awake vs. tired. Furthermore, we used the Dissociation Tension Scale acute (DSS-acute) (Stiglmayr, Braakmann, Haaf, Stieglitz, & Bohus, 2003) to measure dissociative symptoms in the course of the experiment. The MDMQ and the DSS-acute were applied directly before and after the treatment (TSST and placebo-condition) as well as 80 minutes after stress or placebo onset, respectively (the data are available as supplementary material in study I). In addition, prior to and directly after the TSST and placebo-condition all participants rated how challenging, strenuous, controllable, difficult, stressful, new and threatening the particular task was. Furthermore, they were asked for a subjective rating whether they performed well and how involved they felt (the data are shown in study II). The following chapters (3., 4., 5.) provide the original published studies.

3. **STUDY 1** – Psychophysiological stress and memory in BPD and HC

Psychophysiological stress response and memory in borderline personality disorder and healthy controls

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This chapter was published as:

Duesenberg, M., Wolf, O. T., Metz, S., Roepke, S., Fleischer, J., Elias, V., Renneberg, B., Otte, C., Wingenfeld, K. (2019). Psychophysiological stress response and memory in borderline personality disorder. *Eur J Psychotraumatol, 10*(1), 1568134. doi:10.1080/20008198.2019.1568134

https://doi.org/10.1080/20008198.2019.1568134

4. **STUDY 2** – Impact of psychosocial stress on empathy in BPD and HC

Impact of psychosocial stress on empathy in borderline personality disorder and healthy controls

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This chapter was published as:

Wingenfeld, K., Duesenberg, M., Fleischer, J., Roepke, S., Dziobek, I., Otte, C., & Wolf, O. T. (2018). Psychosocial stress differentially affects emotional empathy in women with borderline personality disorder and healthy controls. *Acta Psychiatr Scand, 137*(3), 206-215. doi:10.1111/acps.12856 https://doi.org/10.1111/acps.12856

5. **STUDY 3** – Impact of hydrocortisone on social cognition in HC

Impact of hydrocortisone on empathy and facial emotion recognition in healthy young males and females

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This chapter was published as:

Duesenberg, M., Weber, J., Schulze, L., Schaeuffele, C., Roepke, S., Hellmann-Regen, J., Otte, C., Wingenfeld, K. (2016). Does cortisol modulate emotion recognition and empathy? *Psychoneuroendocrinology, 66*, 221-227. doi:10.1016/j.psyneuen.2016.01.011

https://doi.org/10.1016/j.psyneuen.2016.01.011

6. GENERAL DISCUSSION

In the subsequent sections, our results about an altered stress regulation in female BPD patients will be integrated in existing empirical evidence (section 6.1). To be able to correctly interpret the findings regarding the impact of stress on higher cognition (memory and social cognition), section 6.2 provides an overview about important links between the stress response and cognitive performance and its connection to BPD. Based on these insights, the subsequent sections (6.2.1, 6.2.2 and 6.2.3) integrate the current findings about the impact of stress on higher cognition from this dissertation in a broader theoretical framework. Before we delve into the interpretation of the results, the following Info Box again subsumes the AIMs and the main results of this dissertation.

Info Box 1: Research questions and main results of the dissertation:

Q-I: How does an acute psychosocial stressor influences the physiological stress-system in female BPD patients, compared to a placebo-condition and compared to female healthy controls?

R-I: *We found a blunted ANS and HPA axis reaction to a psychosocial stressor in female BPD patients, compared to female HC. However, not all physiological markers clearly indicated a blunted reaction*.

Q-II: How does psychosocial stress impact on the memory performance in female patients with a borderline personality disorder compared to a placebo-condition and compared to female healthy controls?

R-II: *We did not find any effects of psychosocial stress on memory in female BPD patients. Surprisingly, also, no effects emerged for healthy females.*

Q-III: How does psychosocial stress affect empathy in female patients with a borderline personality disorder compared to a placebo-condition and compared to female healthy controls?

***R-III*:** *The main result was a group by treatment interaction for emotional empathy. Female BPD patients showed diminished emotional empathy compared to female HC after the psychosocial stressor. Cognitive empathy was not affected by stress.*

Q-IV: Does pharmacologically administered cortisol modulate facial emotion recognition and empathy in healthy young men and women?

R-IV: *We did not find any impact of 10mg synthetic cortisol on emotional or cognitive empathy and no sex effects emerged. According to facial emotion recognition, only subtle emotions (40%) seem to be affected. However, treatment and sex interacted with emotional valences*.

6.1. PHYSIOLOGICAL STRESS RESPONSE IN BPD

Previous studies on the physiological reaction to an acute psychosocial stressor in female BPD patients revealed heterogeneous results as some showed a blunted increase of physiological markers, whereas some did not find any differences between groups or even higher values (e.g. Aleknaviciute et al., 2016; Ehrenthal et al., 2018; Lyons-Ruth et al., 2011). The latest data on this topic derive from a quantitative meta-analysis underlining the assumption of a blunted HPA axis reaction in BPD, however, this meta-analysis did not comprise conclusions about an altered ANS system (Drews et al., 2018).

Our results are roughly in line with the assumption of a blunted stress reactivity for both stress-systems in female BPD patients. We calculated the contrasts between pre and post TSST levels for cortisol and alpha-amylase and only revealed a significant increase of hormone levels between the two measurement points for healthy controls. In BPD patients the slope of the increase only achieved trend level. These results are supported by a significant increase in diastolic blood pressure after TSST compared to the placebo-condition in HC. Changes in the BPD group again were on trend level. However, results on systolic blood pressure did not differ between groups. Our data on a relatively large and well-matched sample are interesting since they might point to the necessity of a more flexible and complex explanation of heterogeneous findings among studies.

As already stated in section 1.1, CT/ACE is a highly frequent phenomenon in BPD and contributes to a variety of BPD specific symptoms (Gunderson et al., 2018; Zanarini et al., 1997; Zanarini et al., 2002). It is suggested that on a neuroendocrinological level, CT/ACE challenges the neuroendocrine stress-system in vulnerable neurodevelopmental stages, leading to a chronic *allostatic load*, which in turn provokes a potential reduction of the negative feedback sensitivity of the HPA and the ANS over time (Danese & McEwen, 2012; Rinne et al., 2002; Wingenfeld, Spitzer,

Rullkötter, et al., 2010). This withdrawal has been interpreted as a protective mechanism against unpredictable and chronic environmental threats (Danese & McEwen, 2012). As outlined above, the stress response naturally follows an up- and downregulation by innervating different receptors and their interaction in varying points in time (Joëls et al., 2011; Joëls et al., 2012). Since the downregulation of the stress-response is predominantly associated with the GR (de Kloet et al., 2019), a reduced feedback-sensitivity of the HPA axis might in turn be caused by a reduced sensitivity of the GR (Juruena, 2014). On the one hand this results in an imbalance between GR and MR in favor for MR function. On the other hand, stress diminishing and adapting effects via genomic and non-genomic GR expression are reduced. This in turn might open out into an increased baseline activity in concert with a blunted stress reaction and resemble a dysfunction in stress restoring (de Kloet et al., 2019; Juruena, 2014). Results in healthy individuals with a history of CT/ACE confirm the link between CT/ACE and stress axes activation by expressing a blunted reaction to a psychosocial stressor (Lovallo, Farag, Sorocco, Cohoon, & Vincent, 2012; Voellmin et al., 2015; Zhang et al., 2019). As outlined in 1.2.1.4., Rinne et al. (2002) used the DEX/CRH test to innervate the negative feedback-system of the HPA axis in BPD and revealed that female BPD patients who experienced CT/ACE showed lower suppression rates of the released cortisol compared to female BPD patients with non or a mild CT/ACE history. Carvalho Fernando et al. (2012) confirmed these findings and additionally revealed that the data are rather explainable by CT/ACE than by the BPD symptomatology itself.

These assumptions were recently emphasized by growing evidence on genetic variations and epigenetic[5] alterations in BPD patients and individuals with a history of CT/ACE, which would reflect the biological aspect of Linehan's aetiopathological model (Linehan, 1993). Since there is a wide variety in genetic and epigenetic research on BPD and CT/ACE, this subsection focuses on the most

[5] **Epigenetics:** According to Greally (2018): *"Today, the most common definition of the word is a back-translation of 'epi' (upon, above, beyond) and 'genetic' (DNA sequence), referring to a layer of information that exists beyond that encoded in the DNA sequence, thereby making the genome function distinctively in different cell types."* (p.207)

prominent findings in recent years (Prados et al., 2015). Martin-Blanco et al. (2016) as one of the first, detected an association between a *corticotropin releasing hormone receptor* gene (*CRHR1*) haplotype and the risk to develop a BPD. The *CRHR1* represents a pituitary receptor which mediates the stimulation of CRH and in turn the HPA axis activation. Deficits in *CRHR1* might lead to a disturbed HPA axis and thus a dysregulated stress response. Interestingly, Martin-Blanco et al. (2016) further showed that *CRHR1* is also linked to experiences of CT/ACE. 84% of the BPD patients were female. The second important genetic finding refers to the *FKBP5* polymorphisms, which is also frequently associated with BPD patients and with CT/ACE (Amad, Ramoz, Peyre, Thomas, & Gorwood, 2019; Gunderson et al., 2018; Martín-Blanco et al., 2016). The *FKBP5*-gen codes for a protein that acts as a co-chaperone which regulates the sensitivity of the GR to cortisol by binding to the receptor and decreases its affinity to glucocorticoids (Binder, 2009). A polymorphism of this protein coding gene has been found to result in an upregulation of *FKBP5* which leads to a chronic reduction of the affinity (Amad et al., 2019; Numan, 2015; Schmitt & Falkai, 2016). Hence, the negative feedback sensitivity is reduced due to altered GR expression, and higher levels of glucocorticoids are needed to successfully operate the HPA axis, which indirectly fits to our data in the BPD sample (Numan, 2015). Finally, the GR coding gene itself, namely *NR3C1*, has been found to show an increased methylation in BPD populations and in individuals with a history of CT/ACE (Perroud et al., 2011, 94% female BPD; Prados et al., 2015, 91% female BPD). Interestingly, Perroud et al. (2011) further show that the severity of CT/ACE is positively associated with the degree of *NR3C1* methylation. Gene methylation reflects a powerful epigenetic mechanism, where parts of the genetic information are inactivated or activated by adding or removing of a methyl group to the DNA. This mechanism might also contribute to a reduced or, at least altered, GR sensitivity (Bommarito & Fry, 2019).

In sum, it becomes obvious that a complex gene by environment (G X E) interaction is capable of substantially changing the stress-system in individuals (Agorastos, Pervanidou, Chrousos, & Baker, 2019). Furthermore, an elevated baseline activation in concert with a blunted reaction seems likely in the light of a reduced feedback sensitivity of the HPA axis, possibly due to GR alterations. These assumptions are in line with our data of a blunted HPA axis and ANS system in female BPD patients and confirm other studies who found similar results (e.g. Aleknaviciute et al., 2016; Scott et al., 2013). However, contrasting results in this field exist and the following paragraph provides a possible explanation for this phenomenon.

The above-mentioned genetic vulnerabilities and CT/ACE do not inevitably result in a BPD symptomatology. But rather constitute a broad predisposition for the development of multiple mental disorders (e.g. Assary, Vincent, Keers, & Pluess, 2018; Tsuang, Bar, Stone, & Faraone, 2004). Interestingly, recent data suggest that the type of trauma, the point in time and duration of the traumatic event within a child's development also account for different alterations in the stress-system (Agorastos et al., 2019; Agorastos et al., 2018; Cassiers et al., 2018; Hughes et al., 2017). Agorastos et al. (2018) further postulate that varying CT/ACE in different developmental stages might even result in hyper- or hypoactivity of the HPA axis in later life. This environmental risk factor might additionally challenge genetic and epigenetic vulnerabilities, which also vary across individuals (e.g. Agorastos et al., 2019). Differences between studies in the field of stress and borderline personality disorder might become explainable since not the BPD per se but a complex interplay of CT/ACE and genetic vulnerabilities, at least in part, moderate the alteration in the stress-system.

Furthermore, these assumptions also lead to the importance of co-morbidities in BPD. CT/ACE and genetic variations are also strongly associated with major depression (e.g. Heim & Binder, 2012; Nugent, Tyrka, Carpenter, & Price, 2011; Papale, Seltzer, Madrid, Pollak, & Alisch,

2018; Wang, Shelton, & Dwivedi, 2018) and the posttraumatic stress disorder (e.g. Hawn et al., 2018; McGowan, 2013; Mehta & Binder, 2012; Wang et al., 2018), two mental disorders which are highly linked to BPD (e.g. Gunderson et al., 2018; Pagura et al., 2010; Rinne et al., 2002; Wingenfeld et al., 2013) . Studies show that patients with a major depression predominantly express a similar pattern of an elevated stress-system in concert with a blunted reactivity to acute stress like BPD patients, whereas PTSD patients rather show the opposite pattern (Agorastos et al., 2019; Rohleder, Wolf, & Wolf, 2010; Wingenfeld, Spitzer, Rullkötter, et al., 2010). Interestingly, PTSD as a co-morbidity attenuated the response of female BPD patients to the DEX/CRH test in the study by Rinne et al. (2002), which was confirmed by Wingenfeld et al. (2007) who also used the DEX/CRH test and found less suppression in female BPD patients but only in those with low PTSD symptomatology. Moreover, in our own data the BPD patients with a co-morbid PTSD showed an elevated diastolic blood pressure compared to BPD patients without PTSD. This finding somewhat underlines the assumption of varying activation patterns between mental disorders and fits well to Agorastos et al. (2018) suggestion of a hypo- or hyperactivation of the HPA axis due to varying CT/ACE and genetic vulnerability. Wingenfeld and Wolf (2015) finally postulated that at least two BPD subtypes might exist. One with a focus on traumatic symptoms and one with predominantly affective alterations, which again underlines possible differences due to co-morbidities and the importance of a more flexible view on BPD symptomatology.

In sum, an elevated baseline activation together with a blunted reaction seems likely in the light of a reduced feedback sensitivity of the HPA axis, possibly due to a reduced GR sensitivity. These assumptions are in line with our data of a blunted HPA axis and ANS system in female BPD and confirm other studies who found similar results (e.g. Aleknaviciute et al., 2016; Scott et al., 2013). Furthermore, suggested G X E interactions also support our data. However, differences in existing studies might also be due to G X E interactions in vulnerable developmental phases in

concert with occurring co-morbidities, which needs to be kept in mind when interpreting BPD data.

6.2. IMPACT OF STRESS ON HIGHER COGNITION

The above-mentioned assumptions resemble the complex development and basic understanding of an altered stress regulation in female BPD patients. In the following sections, the results of this dissertation regarding the impact of stress on higher cognition in female BPD patients will be discussed. To be able to interpret the data against the background of an altered stress regulation, several aspects need to be highlighted, before we delve into the cognition data.

First, and as depicted in section 1.3.1.1, for healthy controls there is evidence that the impact of stress hormones on the brain is concentration-dependent and therefore a certain amount of hormones and neurotransmitters are needed to act in concert to evoke changes in e.g. neuronal excitability (Joëls, 2006; Joëls et al., 2018). Wolf (2017) further postulates an inverted U-Shape dose-response relation for the stress-hormones which underlines the importance of a well-orchestrated interaction of the substances. Only with an optimal dosage of catecholamines and glucocorticoids, a successful up and downregulation of the stress response seems possible. As outlined in section 6.1, female BPD patients predominantly suffer from a diminished HPA axis and ANS response to acute stress. Therefore, one could suggest that on the one hand the released stress hormones in BPD might not reach a certain threshold and an impact on higher cognition is altered. On the other hand, the reduced feedback sensitivity of the HPA axis, possibly due to GR dysfunction, might result in a MR:GR imbalance and require even higher dosages of neurotransmitters to operate.

A second aspect relates to the well-orchestrated chronology or time-profile over which catecholamines and glucocorticoids alter neuronal excitability and brain site connectivity (see also section 1.3.1.1) (Joëls et al., 2018). In a nutshell, the catecholamines of the ANS are the first to affect

cerebral networks and are suggested to enhance the connectivity of the salience network (SN), especially by increasing amygdala activity. Several minutes later, the glucocorticoids from the HPA axis also reach the brain and seem to reinforce the effects of the catecholamines by enhancing the excitability of the amygdala and the hippocampus neurons via glutamatergic activation, whereas further diminishing PFC activity. This effect is predominantly moderated by noradrenaline and non-genomic MR effects and shifts the memory-system from complex cognitive processes to more habitual coping mechanisms (Quaedflieg & Schwabe, 2018; Schwabe, 2017). Genomic and non-genomic GR effects in turn predominantly seem to downregulate the stress response by diminishing the activation of the SN and reinstate the activation of the central executive network (CEN), primarily represented by the PFC. Studies on cellular hippocampus and amygdala tissue confirm these assumption as they show that synaptic activation via noradrenaline is mediated by glucocorticoids contingent on the dose and the chronology of both neurotransmitters (Krugers et al., 2012). Since female BPD patients might suffer from a reduced sensitivity of the negative feedback-loop of the HPA axis, one could assume that this balanced interplay between the neurotransmitters and their interaction with several brain sites is impaired which in turn could lead to changes in higher cognitive abilities compared to HC.

Third, there is growing evidence that BPD patients suffer from structural and functional alterations in neuronal networks, which are crucial for higher cognitive abilities. First, on a structural level, there is growing evidence for a volumetric reduction of the hippocampus, the amygdala (Nunes et al., 2009; Ruocco, Amirthavasagam, & Zakzanis, 2012; Schmahl, Vermetten, Elzinga, & Douglas Bremner, 2003; Tebartz van Elst et al., 2003) and even the PFC (Brunner et al., 2010) in BPD. Again, most of the participants were female. On a functional level, most regions identified in BPD as being impaired affiliate with fronto-limbic circuits (Duque-Alarcón, Alcalá-Lozano, González-Olvera,

Garza-Villarreal, & Pellicer, 2019). For instance, data indicate that the functional connectivity[6] (FC) between the limbic structures to the prefrontal cortex is diminished in BPD, which is associated with less cognitive control of emotional responses (Krause-Utz, Winter, Niedtfeld, & Schmahl, 2014; New et al., 2007, mixed male and female BPD sample). Moreover, Minzenberg, Fan, New, Tang, and Siever (2007) found changes in the fronto-limbic activity with an exaggerated amygdala response in BPD patients, while they processed fearful stimuli. In a comprehensive meta-analysis, Schulze, Schmahl, and Niedtfeld (2016) further showed that BPD patients express an hyperactivation of the amygdala in concert with a blunted response of the dorsolateral PFC to negative stimuli. In one of our own study we recently found a reduced resting state functional connectivity (RSFC) between the hippocampus and the dorsomedial PFC in female BPD patients (Metz, Fleischer, Grimm, et al., 2019). Moreover, Doll et al. (2013) revealed a decreased functional connectivity in the central executive network (CEN) and an increased FC within the salience network (SN). Furthermore, the authors found an imbalance between these two networks with a shift to salience network connectivity in BPD patients. This is in line with Schulze, Schulze, Renneberg, Schmahl, and Niedtfeld (2019) who conducted a comparative meta-analysis and detected neural correlates for BPD, MD and PTSD patients. According to BPD, the authors found a hyperresponsive amygdala and a diminished posterior parietal cortex, which is associated with impulsive behavior and is suggested to be a crucial part of the CEN.

It is worth mentioning that the fronto-limbic circuits and the balance between the CEN and the SN first are crucial for higher cognitive abilities, second seem to be altered during a stressful situation in HC and third might represent the neuronal networks, where the most differences in brain function in BPD arise. Interestingly, there is growing evidence that the above outlined

[6] **Functional Connectivity (FC):** Functional connectivity is defined as the statistical relationship between the time series of specific physiological signals according to different brain sites. Techniques like functional magnet resonance imaging are used to detect FC. It is suggested that synchronized brain activity in different regions reflect reciprocal interaction (Ellenbroek & Youn, 2016; Stephan & Friston, 2009).

volumetric changes and dysfunctional neuronal circuits in BPD have also been associated with a history of CT/ACE (Dahmen et al., 2018; Fan et al., 2014; Gee et al., 2013; Kaiser et al., 2017; Silverman, Schulz, & Cullen, 2016) and its connection to the mentioned genetic vulnerabilities (e.g. Matosin, Halldorsdottir, & Binder, 2018; Pagliaccio et al., 2013; Pagliaccio et al., 2015). Figure 7 illustrates this hypothetical model of an altered HPA axis in concert with structural and functional brain sites dysfunctions.

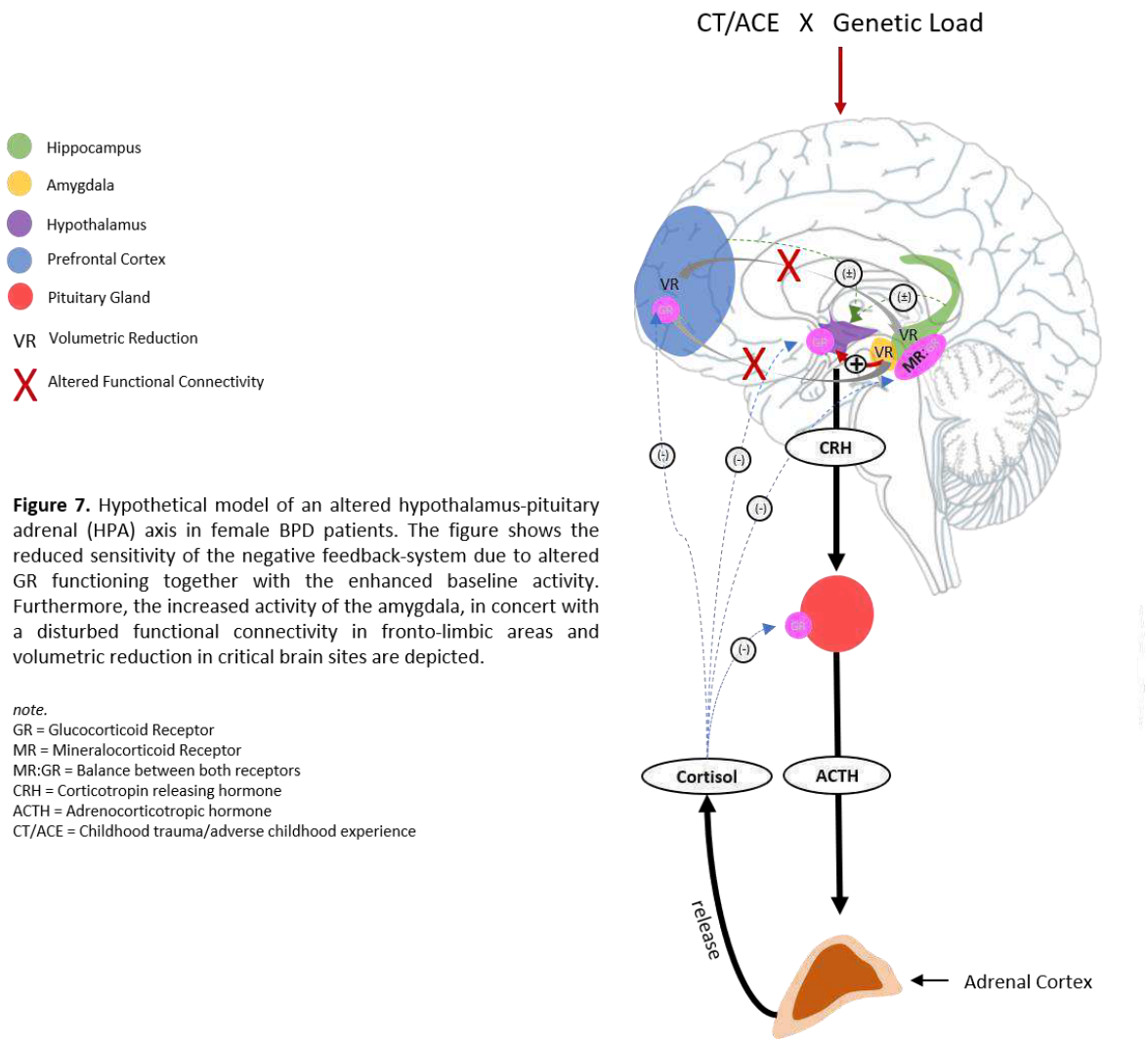

Figure 7. Hypothetical model of an altered hypothalamus-pituitary adrenal (HPA) axis in female BPD patients. The figure shows the reduced sensitivity of the negative feedback-system due to altered GR functioning together with the enhanced baseline activity. Furthermore, the increased activity of the amygdala, in concert with a disturbed functional connectivity in fronto-limbic areas and volumetric reduction in critical brain sites are depicted.

note.
GR = Glucocorticoid Receptor
MR = Mineralocorticoid Receptor
MR:GR = Balance between both receptors
CRH = Corticotropin releasing hormone
ACTH = Adrenocorticotropic hormone
CT/ACE = Childhood trauma/adverse childhood experience

Further results of this dissertation regarding the impact of stress on higher cognition abilities in female BPD patients will now be discussed in the light of the above outlined assumptions.

6.2.1. Impact of stress on memory in BPD and HC

BPD

The importance to investigate in acute psychosocial stress effects on memory performance in BPD not only derives from the lack of studies in this field but is also based on remarkable and paradox findings by Wingenfeld et al. (2013). The authors found that pharmacologically administered cortisol (predominantly GR agonist) resulted in an increase of memory retrieval (semantic and autobiographic) and working memory performance in female patients with BPD. Healthy controls, though, showed the expected memory impairment in all domains. Furthermore, BPD patients with a co-morbid PTSD showed the same pattern, whereas a co-morbid major depression resulted in missing effects. Interestingly, the data of the present dissertation do not support the hypothesis of enhanced memory performance in female BPD patients due to psychosocial stress, compared to a control-condition. We did not find any effect of stress on memory performance in female BPD patients.

The psychosocial stressor in the present dissertation triggered a slightly blunted endogenous release of stress-hormones in female BPD patients and therefore several aspects might account for missing effects on memory performance. Although the blunted reaction of the stress axes was only subtle, one could suggest that the quantity of noradrenaline and adrenaline might not have reached a required threshold to initially alter amygdala excitability (Joëls, 2006). This in turn prevents the modulation of memory-systems around the hippocampus and the PFC (Quaedflieg & Schwabe, 2018). Furthermore, the BPD patients are suggested to suffer from a reduced sensitivity of the negative feedback-system of the HPA axis due to a GR dysfunction (Wingenfeld, Spitzer, Rullkötter, et al., 2010). The blunted cortisol release in turn might not have been sufficient to alter the stress-system due to the elevated need for cortisol. Thus, the MR:GR imbalance on the one hand would not have been restored. On the other hand, diminishing effects of the stress response due to an

intact GR would be missing. This is in line with epigenetic assumptions on the FKBP5 co-chaperone and the higher need for stress-hormones to successfully interact (Numan, 2015). Finally, a concerted interplay between catecholamines and glucocorticoids might be reduced or even absent due to the blunted reaction, since an initial ANS activation and a subsequent boost of neuronal excitability due to glucocorticoids are missing. All mentioned explanations would suggest that the female BPD patients' stress-system would not have been changed through stress, since the released hormones were not sufficient or did not act in chronology. This might explain the missing differences between the TSST and the placebo-condition regarding memory performance in our female BPD sample.

Based on the outlined aspects of our results and of stress in female BPD patients (section 6.2), differences between Wingenfeld et al. (2013) and the results of this dissertation might become explainable. Wingenfeld et al. (2013) administered 10 mg of synthetic cortisol which mainly acts on the GR. As described, the GR plays a crucial role in regulating the recovery phase from a stress response, predominantly via GRs expressed in the hippocampus and via a balanced MR:GR activation (de Kloet et al., 2019; Joëls et al., 2018). In BPD, this sensitivity seems to be diminished. One could speculate that 10mg of hydrocortisone resemble a high add-on of glucocorticoids. Subsequently, the HPA axis activation and in turn a dysfunctional connectivity between the fronto-limbic circuits and the shift to the salience network has been normalized in the BPD patient group for a short term. This might be due to enhanced hippocampus long term potentiation. A study by Champagne et al. (2008) who tested rodents with and without CT/ACE experience showed that corticosterone administration enhanced hippocampal long-term potentiation[7] (LTP) in rodents with a history of CT/ACE, whereas it impaired LTP in rodents without CT/ACE. Oomen et al. (2010)

[7] **Long-Term Potentiation (LTP):** Long Term Potentiation is a well-established neuronal model for learning and memory processes. It was first described for the hippocampus and reflects prolonged and activity dependent synaptic plasticity. This sustained plasticity is suggested to facilitate the storage and editing of memory (Byrne, 2017; Byrne, Heidelberger, & Waxham, 2014).

confirmed these results by testing rats which were maternally deprived. In addition to enhanced long-term potentiation due to high levels of corticosterone the contextual learning was improved in these rats. Furthermore, Pillai et al. (2018) again showed the same pattern in rats and with an object in context learning task. Deprived rats showed enhanced performance after corticosterone. Interestingly, Oomen et al. (2010) postulated that CT/ACE might prepare an organism to show optimal performance in high stress situations. In one of our own fMRI studies in female BPD patients, we recently revealed that severity of CT/ACE positively correlated with the effects of administered hydrocortisone on activation in the prefrontal cortex (Metz, Fleischer, Gärnter, et al., 2019). The data also confirm an association of hydrocortisone with the activation of the CEN in female BPD patients. These assumptions are further disentangled by results on the impact of single MR stimulation. Wingenfeld et al. (2015) found that MR stimulation led to increased working memory but impaired verbal and visuospatial memory retrieval in female BPD patients. MR activation in this BPD sample seemed to enhance PFC related functions but impaired hippocampus related domains. According to the authors, an MR:GR imbalance in the hippocampus due to a reduced GR sensitivity and due to G X E but intact MR:GR balance in the PFC might clarify the results, which is in line with the suggestions of this dissertation. Studies in patients with affective disorders and schizophrenia in humans actually confirm the existence and the aberration of MRs in the PFC (Qi et al., 2013; Xing, Russell, Webster, & Post, 2004). Furthermore, Fleischer et al. (2015) did not find any impact of MR activation on autobiographical memory retrieval in female BPD patients, which again is, at least party, hippocampus-based (Cabeza & St Jacques, 2007; Greenberg et al., 2005). Thus, MR related PFC functions might be intact in female BPD patients, but hippocampus-based abilities seem to be diminished resulting in decreased or absent effects.

Together, these findings on the one hand support the idea of an equilibration of the salience and central executive network in female BPD patients due to high add-on cortisol, which in turn

results in a normalization of the memory function. On the other hand they fit well to an altered MR:GR balance hypothesis and a reduced sensitivity of the negative feedback-system of the HPA axis in concert with a higher baseline arousal due to a reduced GR sensitivity and due to CT/ACE (Oitzl et al., 2010). Figure 8. illustrates the hypothetical impact of a GR agonist, a MR agonist and a psychosocial stressor on neuronal networks and memory in female BPD patients.

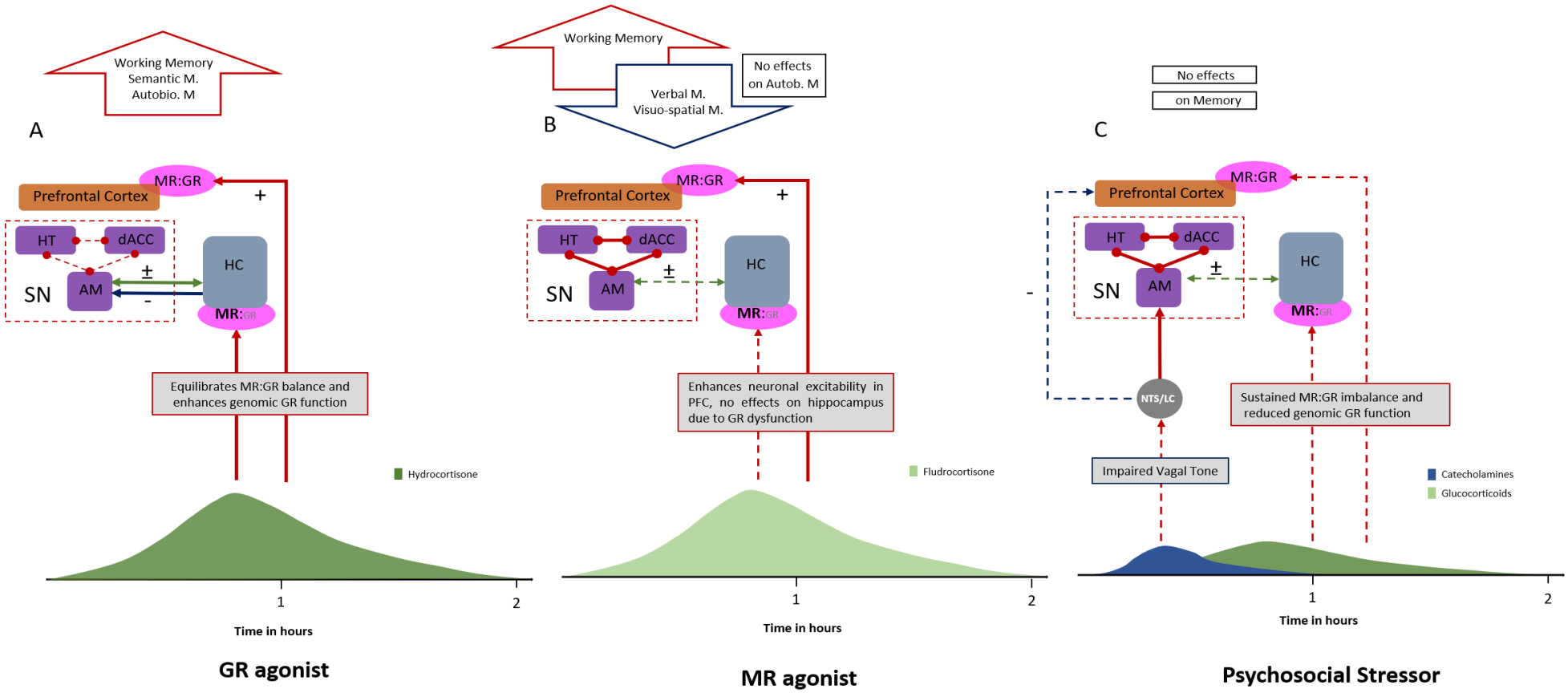

Figure 8. Hypothetical model of the impact of different stressors on different memory domains in female BPD patients. **A.** *Hydrocortisone:* Equilibrating the MR:GR imbalance in the hippocampus and enhances PFC excitability. Potential balancing of the SN and the CEN (not fully depicted in figure 8). **B.** *Fludrocortisone:* Enhances neuronal excitability in the PFC via MR activation. Insufficient to equilibrate the MR:GR imbalance in the hippocampus and limbic areas. SN excitability is still enhanced, therefore HC based memory is diminished. **C.** *Psychosocial stress:* The blunted endogenous reaction to a naturalistic stressor is insufficient to initially activate the amygdala and subsequently balance the MR:GR in the hippocampus. Thus, the psychosocial stressor does not reach an elevated threshold due to a reduced sensitivity of the negative feedback-system of the HPA axis, which in turn explains missing effects on memory. It is worth mentioning that A and B assume that no catecholaminergic effects emerged.

note. HT = Hypothalamus, dACC = dorsal anterior cingulate cortex, AM = amygdala, HC = Hippocampus, MR = mineralocorticoid receptor, GR = glucocorticoid receptor M = memory NTC/LC = nucleus tractus solitarius/locus coeruleus, CEN = central executive network

HC

In addition, no effects of acute stress on memory in healthy women was revealed, which is surprising since impairing effects of stress on memory seems to be a robust finding in HC (de Quervain et al., 2016; Wolf et al., 2016; Wolf, 2009). Several aspects of our sample might contribute to these results. First, these findings might be due to the matching of the sample. Most other studies investigating the impact of psychosocial stress or stress hormones on memory predominantly recruited student samples (e.g. Cornelisse, van Stegeren, & Joels, 2011; Luethi, Meier, & Sandi, 2009; Schoofs, Preuß, & Wolf, 2008), which represent a highly selected population in terms of cognitive functioning and motivation. Healthy women in our study were matched to the female BPD sample in matters of years of education, which reflects a wide educational diversification and might contribute to similar performances between groups.

Second, studies investigating the impact of acute stress on memory predominantly revealed a declining effect in male participants (Kuhlmann, Piel, & Wolf, 2005; Schoofs et al., 2008; Schoofs, Wolf, & Smeets, 2009). Other studies in women did not show any effect of stress on memory (Wolf, Schommer, Hellhammer, McEwen, & Kirschbaum, 2001). It is assumed that the different phases of the menstrual cycle and the intake of oral contraceptives might diminish or even prevent impairing effects of cortisol in memory (Espin et al., 2013; Merz & Wolf, 2017; Schoofs & Wolf, 2009). To control for group heterogeneity, in our study the individuals of the female HC sample were matched to the phase of the menstrual cycle or to OC intake of the corresponding BPD patient. Thus, most of the participants were tested during the luteal-phase or while using OCs, which might have diminished the effects of stress in memory. However, oral contraceptive did not show any confounding impact on the memory results.

Moreover, it is worth mentioning that there were no overall differences in memory performance between BPD patients and HC except for negative trials in the working memory task, where female BPD patients performed worse than HC, independent of treatment. A comprehensive and recently conducted meta-analysis showed that BPD patients with a higher percentage of co-morbidities, especially major depression, perform worse in neurocognitive task, than BPD patients with less co-morbid disorders. Interestingly, PTSD and anxiety disorders as co-morbidities did not account for impaired neurocognitive performances in BPD (Unoka & J. Richman, 2016). Since an acute major depression was an exclusion-criteria in this dissertation, one could suggest that our BPD sample might not have suffered from heavy cognitive impairments. Thus, absent differences between BPD and HC in our study are possibly be due to a-priori monitored affective co-morbidities. Finally, one could argue that the used memory tasks were not sensitive enough to detect differences between groups. However, the same tasks were conducted in Wingenfeld et al. (2012) and clearly distinguished between BPD and HC.

In sum, the blunted stress response in concert with a reduced sensitivity of the negative feedback-system of the HPA axis might explain the missing effects of stress on memory in female BPD patients. Enhancing effects in the study by Wingenfeld et al. (2013) are possibly due to a high add-on of cortisol which diminished the overshooting salience network and restored balance between the SN and the CEN in BPD for a short time. Furthermore, the influence of the menstrual cycle or the intake of oral contraceptives and a heterogeneous sample in matters of education might account for missing effects of acute psychosocial stress on memory in our female HC subsample. Finally, missing differences in cognitive performance between groups possibly rely on an a-priori control for affective disorders.

6.2.2. Impact of stress on empathy in BPD and HC

Destructive relationships and feelings of being abandoned are core features of the BPD (American Psychiatric Association, 2013). The daily routine in BPD patients can further comprise a variety of potential threatening situations, which are often connected to social interactions (e.g. Jeung & Herpertz, 2014; Lazarus, Cheavens, Festa, & Rosenthal, 2014). Since the acute physiological stress response might be altered, it seemed worthwhile to investigate in a potential interplay between social cognition and experienced stress. To date only two studies challenged the stress-system in BPD patients (all female samples) and examined social cognition. Using a pharmacological approach, Wingenfeld et al. (2014) administered a MR agonist and reveled increased emotional empathy in female BPD patients, whereas no effect emerged for cognitive empathy. Deckers et al. (2015), in turn provoked a full-blown stress response via a psychosocial stressor (TSST) and tested facial emotion recognition in their female BPD sample. They also revealed an increased performance in their sample, however, the TSST did not provoke a stress response in the BPD group and the authors could not separate the findings from practice effects. Interestingly, the female BPD sample in this dissertation showed lower scores in emotional empathy after TSST compared to the healthy individuals (group by stress interaction). Post-hoc tests to compare emotional empathy after psychosocial stress and after the placebo-condition did not reach significance. However, this might be due to the sample-size and a lack of power as the effect sizes are medium. The BPD and HC sample did not differ in matters of cognitive empathy after psychosocial stress and compared to the control condition. The most important difference, besides the psychosocial stressor in comparison with the MR stimulation might be the time between the stressor and the conducted social cognition task.

The other two studies tested empathy and facial emotion recognition directly after the TSST (Deckers et al., 2015) or during full activation of the MR (Wingenfeld et al., 2014). In the present

dissertation, the empathy task started approximately 65 minutes after psychosocial stress. Based on section 6.2, one could suggest that not only the fast acting ANS in concert with non-genomic MR activations moderate social cognition, but also non-genomic GR and slower acting genomic GR effects began to act and might play a role in emotional empathy. In line with this argument, De Kloet et al. (2018) postulated that the GR not only regulates the stress recovery by facilitating memory consolidation and integrate new experiences in the persons history, but also might support altruistic behavior in HC and the search for social bonding to seek help in threatening situations. One could suggest that ANS and MR activation support a first attention shift to coping mechanisms and enhance the ability to feel for another person or the ability to detect emotions in facial expressions which is in line with Wingenfeld et al. (2014) and Deckers et al. (2015). Subsequently, an intact GR in concert with a previously activated ANS and MR could promote a long-lasting increase in emotional empathy to process and cope with the experienced stressful situation by e.g. innervating interactional partners. This is in line with the so called "*tend and be friend*" hypothesis by Taylor et al. (2000). The authors state that besides the "*fight and flight*" response, enhanced prosocial behavior and in turn social cognition might also be a reasonable response to acute stress, since it bonds to other individuals as a coping mechanism.

In female BPD patients, however, the ability to feel for another person (emotional empathy) seems to be inhibited by acute psychosocial stress, only when the task is conducted with a delay of more than one hour, which fits well to the idea of an intact ANS and non-genomic MR system and a reduced GR sensitivity. Deckers et al. (2015) and Wingenfeld et al. (2014) confirm the assumption of an intact initial moderating role of the ANS and MR activity. A reduced GR sensitivity in concert with an altered negative feedback-system of the HPA axis might in turn result in changes of the orchestrated chronology in receptor functioning. Therefore, one could suggest that late genomic driven GR effects and / or a MR:GR balance in limbic areas are disrupted. The downregulation of the

stress response is inhibited, and fronto-limbic circuit activation cannot be normalized. As a consequence, the BPD patients rather remain in a sustained "*fight or flight*" mode after acute psychosocial stress and in turn are either not able to adequately detect or don't even experience a feeling for another person. Interestingly, our data on subjective mood ratings before and after psychosocial stress fit well to the idea of a prolonged "*fight or flight*" response in female BPD patients (see also Info Box II). The patients showed higher mood disturbances after stress, compared to HC and this effect outwore the whole investigation. The HC subjective mood disturbances on the other hand, returned to baseline until the end of the investigation. These data support the assumption of a disturbed emotion regulation after stress in concert with a dysfunctional downregulation (reduced sensitivity of the negative feedback-system) and in turn might result in a reduced capacity to feel for another person in female BPD patients (emotional empathy).

On a neurological level, Duque-Alarcón et al. (2019) conducted an fMRI study and tested social cognition in BPD patients with an ecologically valid task. They found a relation between a diminished connectivity in fronto-limbic circuits and impairments in social cognition performance, which was mainly driven by the activity of the amygdala. As outlined above, the amygdala reflects the core area of the salience network, which is suggested to be hyperreactive in BPD patients (Schulze et al., 2019). Since GR and MR are both highly expressed in the amygdala, one could speculate that a MR:GR imbalance also accounts for the amygdala and in turn for an altered stress regulation due to a reduced GR sensitivity. This is in line with a study by Henckens, van Wingen, Joëls, and Fernández (2010) who also administered 10mg of hydrocortisone to a group of healthy male participants and scanned their brain-activity 75 minutes after pill intake. In addition, the participants saw pictures of happy and fearful faces. Cortisol suppressed the amygdala activity to both emotions due to genomic GR activity. This effect might be disrupted in female BPD patients.

In sum, the amygdala and SN related brain areas might be more sensitive to even a blunted response to stress, since we detected a disruption of emotional empathy, whereas memory was not affected in BPD. However, we did not test memory after one hour and therefore cannot derive conclusions about a possible late impact on memory performance. Furthermore, fast acting MR receptor functioning and ANS activity might be intact in female BPD patients. Due to impairments of the downregulation, adapted from the GR, female BPD patients persist in a prolonged condition of *"fight or flight"* and in turn show impairments in social interactions. These assumptions fit well to clinical observations in BPD, were disruptive and vengeful social interactions are a common phenomenon and might, at least in part, be due to the above outlined impaired downregulation of a stress response in social situations. The subjective mood rating data in this dissertation also support this idea.

Info Box II: Impact of psychosocial stress on subjective mood ratings in female BPD patients and HC

Although existing studies vary in measurements according to subjective mood ratings, results during and after acute stress are highly consistent. Female BPD patients across studies rate their experienced mood disturbances and increased arousal following psychosocial stress as being significantly more severe compared to healthy controls (e.g. Aleknaviciute et al., 2016; Deckers et al., 2015; Nater et al., 2010; Scott, Levy, & Granger, 2013). These effects are predominantly explained by a negative biased attribution in the BPD population and an altered anticipation of upcoming (social) situations. Furthermore, BPD patients across studies report a stronger feeling of being rejected (Chapman, Walters, & Gordon, 2014, ~ 70% female; Renneberg et al., 2012, 87% female), which fits well to mistrustful interactions in BPD. In line with literature and our hypothesis, our female BPD sample also showed higher ratings regarding most subjective rating domains. Interestingly, female BPD patients not only showed an increase in mood disturbance after stress, but during the whole investigation, which underlines differing attribution styles and poor subjective recovery from stress compared to healthy controls (Duesenberg et al., 2019; Wingenfeld et al., 2018). For a detailed description of the subjective mood rating data in this dissertation project, please see Wingenfeld et al. (2018) and the supplemental material from Duesenberg et al. (2019).

6.2.3. Impact of hydrocortisone on social cognition in HC

Several studies so far investigated in the impact of acute stress on social cognition and used a well-established psychosocial stressor to provoke a full-blown stress response in HC. Results across studies predominantly revealed an increase in facial emotion recognition performance (Barel & Cohen, 2018; Deckers et al., 2015; Domes & Zimmer, 2019) and emotional empathy, whereas cognitive empathy seems to be unaffected by stress (Wolf et al., 2015). The research group around Tomova showed that prosocial behavior is enhanced by acute psychosocial stress, however, this effect seems to some extend depend on sex and context (Tomova et al., 2017; Tomova et al., 2019; Tomova et al., 2014). As described in the section above, there is further evidence that single MR activation also enhances emotional empathy in healthy female controls (Wingenfeld et al., 2014). In addition, this dissertation contributes data confirming that a psychosocial stressor enhances emotional empathy in female HC also as a rather prolonged effect, whereas cognitive empathy was unaffected (Wingenfeld et al., 2018, AIM III). Interestingly, effects of a single-dose of hydrocortisone as a predominantly GR agonist on social cognition are missing. To disentangle potential involvements of the receptors we therefore conducted a third study on healthy individuals (AIM IV) and dispensed 10mg of hydrocortisone as a GR agonist or a placebo and subsequently tested cognitive and emotional empathy and facial emotion recognition skills (Duesenberg et al., 2016). We did not find any effect of cortisol or GR reactivity, respectively, on cognitive and emotional empathy in HC. Results regarding the impact of hydrocortisone on facial emotion recognition in males and females showed a complex four-way-interaction (treatment, intensity, sex, emotion). The four-way-interaction showed that male and female participants differently reacted to the hydrocortisone regarding their emotion detection performance of anger and sadness. The most important finding can be zoomed in on the 40 % emotional intensity. At 40% emotional intensity female participants were better in detecting anger than males when taking placebo. This advantage

toward men disappeared in the hydrocortisone condition due to contrasting effects of the stress hormone in males and females. Furthermore, at 40 %, men showed a better performance in detecting sadness than anger in the placebo-condition. This difference also vanished, when taking hydrocortisone. In sum, one could suggest that first, only subtle emotions are affected by hydrocortisone and second that these effects might be sex specific. However, no main effect of hydrocortisone on facial emotion recognition emerged and interactional effects in concert with sex were not unambiguous.

The missing effects regarding emotional and cognitive empathy as a complex social cognitive ability fit well to the assumption that social cognition alterations due to stress predominantly depends on MR activation or on a balanced receptor impact in concert with an optimal temporal profile of HPA axis and ANS activation (Krugers et al., 2012). This is in line with other studies, which tested their participants directly after psychosocial stress approximately 20 minutes after stress onset (Wolf et al., 2015) or during pharmacological stimulation of the MR (Wingenfeld et al., 2014). Based on these considerations and following section 6.2, one could argue that single hydrocortisone administration without a prior increase of catecholamines might have less or even no effect on neuronal activity which leads to missing changes in cognitive and emotional empathy. These assumptions are supported by Kuhlmann and Wolf (2006). The authors tested two groups of healthy young women. Every participant received 30mg of hydrocortisone, whereupon one group experienced a more relaxed experimental setting. In contrast to the other group, the more relaxed participants did not show an impaired memory performance. These effects are in line with an animal study by Okuda, Roozendaal, and McGaugh (2004) who showed that only rats which had experienced emotional arousal (noradrenaline release) due to the experimental setting profit from additional corticosterone in an object recognition memory task. Thus, missing arousal due to the experimental setting and represented by an increase of catecholamines might lead to diminished or

even absent effects of hydrocortisone also on cognitive and emotional empathy as a complex social cognition task. The same argument partly applies for the facial emotion recognition task. However, we found some interactional effects, which also included the treatment factor. Here, one could argue that facial emotion recognition represents a more basic social ability and therefore requires less cognitive effort. As outlined above, Henckens et al. (2010) also administered 10mg of hydrocortisone to a group of healthy male participants and scanned their brain-activity 75 minutes after pill intake. Cortisol suppressed the amygdala activity while the participants saw pictures of happy and fearful faces. Krugers et al. (2012) argued that in the study by Henckens et al. (2010) the experimental setting was arousing enough to provoke a noradrenaline release, which in turn enabled the above mentioned effects. In line with these assumptions, Joëls et al. (2018) recently confirmed that neuronal excitability and suppression of the basolateral amygdala and in turn the moderation of the stress response depends on the dosage of catecholamines and glucocorticoids. Therefore, a small release of noradrenaline due to the experimental setting in concert with a high add-on of exogenous cortisol in our study might only have triggered marginal effects which were sufficient to partly change facial emotion recognition performance but had no impact on empathy.

In sum, we found no effects of 10mg hydrocortisone on cognitive and emotional empathy in young HC. Furthermore, hydrocortisone only impacted on subtle facial emotion recognition (40%) and these effects were sex dependent and heterogeneous. According to Kuhlmann and Wolf (2006), the arousal due to the experimental setting might be crucial for an impact of add-on cortisol on social cognition. Thus, absent effects of cortisol on a complex social cognition task like empathy become explainable by a potential lack of sufficient noradrenergic action prior to cortisol administration. The interplay between cortisol and a subtle noradrenergic release, though, might have been adequate to provoke an ambiguous impact on facial emotion recognition as a more basic

social cognitive ability. However, since we did not measure ANS activation in this study, the outlined assumptions remain speculative.

6.3. STRENGTHS AND LIMITATIONS

In this chapter the strength and limitations for each of the three studies conducted in the dissertation are illustrated. The section is subdivided according to the studies, since the strength and weaknesses vary across the individual investigations.

Study I

A strength of the first study is the complex intraindividual cross-over design, since it is quite robust against interindividual differences between the participants. Furthermore, it allows for an efficient and sufficient data collection in terms of statistical power, especially when recruiting patients with mental disorders. This is further the first study which used a placebo-condition (Het et al., 2009) in concert with a well-established stressor (TSST) to test female BPD patients. Thus, insight can also be drawn from a comparable placebo-condition and does not only rely on data from healthy individuals compared to a mental disorder. Moreover, literature shows that a current major depression and a PTSD differently impact on the stress axes and are frequent co-morbidities in BPD patients (Wingenfeld & Wolf, 2015). Thus, we a-priori excluded all patients with a current major depressive episode and balanced BPD patients with and without a PTSD to account for potential influence.

However, the results also have to be interpreted in the light of several limitations. First, due to practical reasons we only recruited female participants and therefore we cannot transfer our conclusions to male BPD patients or male HC. Only testing females also rises the challenge to mind the menstrual cycle. Most of our participants were tested during the luteal phase (free-cycling

women) or while taking oral contraceptives (OC), which might account for our missing effects on memory performance (e.g. Merz & Wolf, 2017). Furthermore, besides a current MD and a PTSD, BPD patients also frequently suffer from other axis I disorders, which are known to affect the stress axes (e.g. Pagliaccio et al., 2015). For instance, studies have repeatedly shown that anxiety disorders might also play a crucial role in dysfunctional stress regulation (Condren, O'Neill, Ryan, Barrett, & Thakore, 2002; Elzinga, Spinhoven, Berretty, de Jong, & Roelofs, 2010; Faravelli et al., 2012). Despite a comprehensive number of participants, our sample was still too small to detect subgroup differences regarding other co-morbidities. Thus, a potential impact of e.g. anxiety disorder cannot be ruled out. Finally, our BPD sample was not completely medication free. Although there were only little effects of medication intake on stress axes activity (diastolic blood pressure), the majority of the used drugs influenced the serotonin, adrenaline and dopamine balance in our BPD sample. Thus, a potentially mediating effect of medication has to be kept in mind, when interpreting study I.

Study II

Since study I and II comprise the same BPD and HC sample, most of the above-mentioned strength and limitations also account for study II. However, some important differences need to be addressed. It is worth mentioning that we used a well-validated and ecologically valid empathy task in study II (MET). Moreover, the MET consists of two subtests to separately detect emotional and cognitive empathy. Our results in study II confirm the necessity to test for both empathy aspects, since only emotional empathy was affected by stress. A specific limitation of study II is the between subject design. The MET does not exist in a paralleled version and our BPD patient and HC sample had to be differentiated by the first scheduled appointment (TSST or Placebo). Effect sizes in our data suggest that missing effects between the stress and the placebo-condition arise from a small sample size and a lack of power. Furthermore, small effects, especially for cognitive empathy were

also not detectable. Finally, due to the TSST and the placebo-condition, both study I and II had to be designed as single-blinded, which might additionally have an impact on the results.

Study III

The design of the third study allowed us to investigate the impact of a single stress hormone (cortisol) on facial emotion recognition and empathy without any side-effect of other hormones typically released during a naturalistic stress reaction (e.g. catecholamines). We further used the same empathy task, like we did in study II to be able to compare our data across studies. Since there is evidence that sex might influence the cortisol's impact on social cognition (Smeets et al., 2009), we balanced male and female participants across the sample. This enabled us to systematically detect sex effects. However, a major limitation of this study is that, although we balanced our sample regarding sex, we were not able to separate responses from our male and female participants regarding male and female faces in our facial emotion recognition task. Thus, effects due to same or opposite sex faces cannot be ruled out (Hofmann, Suvak, & Litz, 2006). Furthermore, we only tested sadness and anger and studies in the field of facial emotion recognition and stress show that different valences might lead to different results (Barel & Cohen, 2018; Deckers et al., 2015; Domes & Zimmer, 2019). Therefore, integrating more emotional valences would have been important to detect a broader range of hydrocortisone impact. Finally, we did not monitor a potential increase of catecholamines due to the experimental setting, which would have been beneficial to validate whether a missing or a small-sized release account for the absent or heterogeneous effects (Krugers et al., 2012). For a detailed description of the strength and limitations see study III.

6.4. IMPLICATIONS FOR FUTURE RESEARCH

According to the four aims in this dissertation and their strength and limitations, this section deduces implications for future research from the above-mentioned results.

The first aim provides valuable information about the physiological stress-system in female BPD patients in general. However, the results are still ambiguous since the reaction to a psychosocial stressor in BPD was only blunted for some of the measured variables. These data were discussed in the light of varying traumatic events during childhood in concert with epigenetic factors. Therefore, future research should assess traumatic childhood events in detail to be able to interpret potential outcomes on the basis of type of trauma, duration and lifetime chronology. Furthermore, the research on genetic and epigenetic vulnerabilities seems promising, as on the one hand potential predispositions might become detectable. On the other hand, genetic analysis could help to disentangle the impact of CT/ACE on varying symptomatology in later life.

Moreover, the connection between G X E and alterations in the fronto-limbic neuronal networks on the one hand and a reduced sensitivity of the negative feedback-system of the HPA axis due to a possible reduced sensitivity of the GR is an important factor which needs to be focused on in future research. Imaging studies, which use psychosocial stressors in the fMRI might be promising to detect fronto-limbic changes depending on G X E. In line with gene by environment interactions, the focus on co-morbidities seems to be important. According to our data and to Drews et al. (2018) or Wingenfeld et al. (2013) future studies need to systematically assess major depression and PTSD. Both axis one disorders are highly linked to CT/ACE and genetic vulnerabilities on the one hand and to BPD on the other hand (e.g. Wang et al., 2018; Wingenfeld & Wolf, 2015). Finally, besides the possible MR:GR imbalance in BPD, there is growing evidence that the α1, α2 and β receptors of the ANS might also react according to the released dosage of catecholamines and

activate or diminish neuronal excitability (Gibbs & Summers, 2002; Hermans et al., 2014). Thus, in the light of studies showing elevated sympathetic activation with a dampened parasympathetic vagal tone (e.g. Weinberg et al., 2009), one could speculate that an imbalance between α1, α2 and β receptors also account for an altered stress response in BPD.

The second, third and fourth aim of this project focused on the impact of psychosocial stress or a single stress-hormone on higher cognition in female BPD and HC (memory and social cognition). In general, the results highlight the need to further disentangle the temporal pattern and the dosage of different receptor functions in health and disease and its impact on cognition. Study I showed that a blunted reaction to a psychosocial stressor did not change the memory performance in female BPD patients, which contradicts the results by Wingenfeld et al. (2013). The proposed model implicates an altered or diminished GR functionality in concert with impairments of the functional connectivity of the fronto-limbic circuit in BPD patients. These alterations might be "normalized" by high add-on cortisol but remain unaffected by a blunted naturalistic stressor. Thus, future studies should subsequently dispense GR, MR, α and β receptor agonists and antagonist to verify the normalizing effects of an overshooting system by hydrocortisone. It would be promising to combine fMRI studies to detect changing functional connectivity, especially in the fronto-limbic system during e.g. memory tasks under stress. Study II further implies an interesting topic in matters of emotional empathy. As outlined, the GR or MR:GR balance are suggested to also play a role in a prolonged enhancement of emotional empathy, which seems to be disrupted in BPD and might, at least in part, account for vengeful social interactions. Again, blocking or activating the MR and GR alone and in concert with catecholamines before testing emotional and cognitive empathy in future research might shed more light on a possible implication for BPD symptomatology. Moreover, and in line with study III, upcoming investigations need to focus on different time intervals between hormones and memory or social cognition tasks, respectively, to further disentangle the concerted

interplay between stress-hormones and their (non)-genomic actions. Finally, when testing the impact of a single hormone administration on higher cognition, it is advisable to not only assess a marker for the specific hormone e.g. cortisol, but in general to always use markers for other neurotransmitters, which are known to interact on a neuronal level with the target substance, e.g. catecholamines. Differences between studies might become more explainable.

In general, an extensive part of the illustrated studies in this dissertation only tested female BPD patients to reveal alterations in the stress-system and a possible connection to higher cognition. Although female patients are more frequent in the medical care system, e.g. Inoue et al. (2015) showed that there might be important differences between the stress-system in male and female BPD patients. Since the prevalence rate for BPD in the population seems to be equal for males and females, future studies should suggest to also recruit male samples and close this serious gap in existing research.

6.5. CLINICAL IMPLICATIONS

This dissertation also provides some clinical implications. The first study shows that the borderline personality disorder and its varying symptomatology might, at least in part, derive from a complex interplay between CT/ACE and genetic factors. For future diagnostics it might be useful and promising to detect and separate different types of trauma to be able to individualize the present symptomatology. Together with genetic analysis, assessment of the diagnosis could become more specific for every patient, not only for BPD. Furthermore, Study II showed that stress in BPD patients might lead to a prolonged "*fight or flight*" reaction in concert with poor emotional insight (emotional empathy), which fits well to clinical observations of vengeful interactions and disruptive relationships. Thus, study II supports the use of therapeutic approaches which include the practice

of interpersonal skills, stress regulation, emotional insight and validating one's own feelings (e.g. Dialectic Behavioral Therapy, Linehan (2014)).

6.6. CONCLUSION

To summarize, this dissertation provides valuable insight in the physiological stress-system of female BPD patients and its impact on higher cognitive abilities. In line with current research, the BPD patients showed a slightly blunted reaction of both stress axes compared to healthy controls to a well-established psychosocial stressor (Aleknaviciute et al., 2016; Scott et al., 2013). As outlined above, genetic vulnerabilities in BPD in concert with experienced CT/ACE (G X E) might account for an altered negative feedback sensitivity of the HPA axis (Carpenter, Tomko, Trull, & Boomsma, 2012). This reduced sensitivity of the negative feedback-system seems predominantly be due to a reduced GR sensitivity and/or expression of GR relevant genes (Wingenfeld, Spitzer, Rullkötter, et al., 2010). In addition, evidence shows that G X E is also related to a dysfunctional front-limbic connection, which highly overlap with structural and functional neuronal changes in BPD patients (Hart et al., 2017; Kaiser et al., 2017; Schulze et al., 2016; Schulze et al., 2019; van Elst et al., 2003). One could suppose that heterogeneities between studies regarding stress axes alterations in BPD and our slightly ambiguous data are rather explainable by a complex interplay between different genetic vulnerabilities and varying CT/ACE experiences then due to the BPD diagnosis itself. Furthermore, co-morbidities, especially MD and PTSD, and their interactions with G X E are crucial for the interpretation of BPD data in the light of stress.

Furthermore, these assumptions form the basis for the interpretation of our cognition data, since the fronto-limbic circuit and the MR:GR balance are crucial for successful cognitive abilities (Duque-Alarcón et al., 2019; Quaedflieg & Schwabe, 2018). The neurotransmitters of the two stress axes act in a well-concerted chronology and contingent on the released dose within the brain

(Quaedflieg & Schwabe, 2018; Schwabe, 2017). Thus, one could assume that a lower increase of neurotransmitters together with a disrupted negative feedback sensitivity of the HPA axis led to absent differences between the stressful situation and the placebo-condition in female BPD patients. Moreover, these alterations also account for contrary effects of stress on empathy in BPD and HC. The empathy test was conducted approximately one hour after stress onset. Thus, due to a reduced sensitivity of the negative feedback-system of the HPA axis and therefore a disrupted downregulation of the stress-response, female BPD patients showed impaired emotional empathy. Female HCs, though, showed enhanced emotional empathy which is in line with an intact negative feedback-system of the HPA axis and the "tend and be friend" hypothesis (Taylor et al., 2000). Finally, our absent effects of a single administration of cortisol on social cognition in HC also fit well into the outlined model. Since cortisol needs an initial increase of catecholamines to boost neuronal excitability, an exclusive administration of cortisol remains ineffective (Krugers et al., 2012; Kuhlmann & Wolf, 2006). It is worth mentioning that gene by environment interactions and their implication for cognitive changes consist of unlimited possible combinations and therefore might also determine varying changes in cognitive abilities across BPD samples.

To conclude, gene by environment interactions are crucial indicators for HPA axis and ANS alterations in BPD patients and might rather account for differences between studies then the BPD symptomatology itself or co-morbidities. In addition, the aftermath of G X E and alterations in functional connectivity in neuronal network (including changed negative feedback sensitivity) might also contribute to varying results regarding the impact of stress in higher cognition in BPD. Applying neurocognitive models from healthy individuals in combination with recent research about G X E seems promising to integrate interesting results regarding BPD. It is worth mentioning that, even though we looked at a comprehensive set of stress markers and their interactions in this dissertation, the ANS and the HPA axis are accompanied by further psychoneuroendocrinological

systems, like for instance the endocannabinoid system (e.g. Hill & McEwen, 2010; Morena, Patel, Bains, & Hill, 2015), or the dopaminergic system (e.g. Belujon & Grace, 2015; Karkhanis, Rose, Weiner, & Jones, 2016). Thus, although this dissertation provides valuable insight in the stress system and its impact on higher cognition in female BPD patients and HC it represents an extract of the full story. Many questions are still unanswered, but it seems promising to further investigate in the complexity of the stress-system, higher cognitive abilities and their connection to genes and environment, since not only BPD but a wide variety of mental disorders might benefit from deeper insight.

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APPENDIX

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACE	Adverse Childhood Experiences
ACH	Acetylcholine
ACTH	Adrenocorticotropic Hormone
AM	Autobiographical Memory
AMT	Autobiographical Memory Test
ANS	Autonomic Nervous System
BDI	Beck Depression Inventory
BMI	Body Mass Index
BPD	Borderline Personality Disorder
BPS	Borderline Persönlichkeitsstörung
CEN	Central Executive Network
CRH	Corticotropin Releasing Hormone
CT	Childhood Trauma
CT/ACE	Childhood Trauma / Adverse Childhood Experiences
CTQ	Childhood Trauma Questionnaire
DEX	Dexamethasone
DGP	German Psychology Association
DSS acute	Dissociation Tension Scale acute
FC	Functional Connectivity
fMRI	Functional Magnetic Resonance Imaging
G X E	Gene by Environment Interaction
GR	Glucocorticoid Receptor
HC	Healthy Controls
HPA axis	Hypothalamus Pituitary Adrenal axis
HR	Heart Rate
HRV	Heart Rate Variability
LC	Locus Coeruleus
LTP	Long-Term Potentiation

MD	Major Depression
MDMQ	Multidimensional Mood Questionnaire
MET	Multifaceted Empathy Test
mg	Milligram
MR	Mineralocorticoid Receptor
NM	Nano Mol
NSSI	Nonsuicidal Self-Injury
NT	Neurotransmitter
NTS	Nucleus Tractus Solitarius
OC	Oral Contraceptives
PFC	Prefrontal Cortex
PTSD	Posttraumatic Stress Disorder
PVN	Paraventricular Nucleus
RSA	Respiratory Sinus Arrhythmia
RSFC	Resting State Functional Connectivity
sAA	Salivary Alpha Amylase
SCID	Structured Clinical Interviews for DSM-IV
SCR	Skin Conductance
SN	Salience Network
TSST	Trier Social Stress Test
VAS	Visual Analogue Scale
WST	Word Suppression Test

CURRICULUM VITAE

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LIST OF PUBLICATIONS

Duesenberg, M., Weber, J., Schaeuffele, C., Fleischer, J., Hellmann-Regen, J., Roepke, S., Moritz, S., Otte, C., Wingenfeld, K. (2016). Effects of hydrocortisone on false memory recognition in healthy men and women. *Behavioral Neuroscience, 130*(6), 635-642. doi:10.1037/bne0000170

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CONGRESS CONTRIBUTIONS

DGPPN 2015 — Duesenberg, M., Weber, J., Schulze, L., Schauffele, C., Roepke, S., Otte, C. & Wingenfeld, K. (2015). **Beeinflusst Cortisol die soziale Kognition?** Poster at the DGPPN Congress (German Association of Psychiatry, Psychotherapy and Psychosomatics).

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DGPPN 2018 — Nowacki, J., Duesenberg, M., Deuter, C., Otte, C., Wingenfeld, C. (2018). **Späte Effekte von psychosozialem Stress auf das Risikoverhalten**. Poster at the DGPPN Congress (German Association of Psychiatry, Psychotherapy and Psychosomatics).

AUTHOR'S CONTRIBUTION TO THE PUBLICATIONS

1. Duesenberg, M., Wolf, O. T., Metz, S., Roepke, S., Fleischer, J., Elias, V., Renneberg, B., Otte, C., Wingenfeld, K. (2019). Psychophysiological stress response and memory in borderline personality disorder. *Eur J Psychotraumatol, 10*(1), 1568134. doi:10.1080/20008198.2019.1568134

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EIDESSTATTLICHE VERSICHERUNG (statement of authorship)

Ich versichere, dass ich die vorliegende Arbeit selbstständig verfasst habe und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt wurden. Alle Zitate wurden kenntlich gemacht. Die vorliegende Dissertation wurde in keinem vorhergehenden Promotionsverfahren eingereicht und ich besitze keinen Doktorgrad im Fach Psychologie. Die Promotionsordnung der Freien Universität Berlin vom 27.10.1998, zuletzt geändert am 02.12.2008 veröffentlicht im Amtlichen Mitteilungsblatt Nr. 60/2008 ist mir bekannt.

Berlin, den 30. September 2019

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