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Stress-regulating systems and stress-relevant brain regions in posttraumatic stress disorder and borderline personality disorder

- The role of childhood trauma -

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English summary

Posttraumatic stress disorder (PTSD) and borderline personality disorder (BPD) are highly comorbid. Patients with both disorders report the highest likelihood of lifetime suicide attempts and the lowest mental health related quality of life. Given the high likelihood of comorbid PTSD and BPD and the great burden on those affected, mutual biological and behavioural characteristics of both disorders and their causes seem worthwhile investigating. The current dissertation project aims at further describing overlapping and distinct alterations in stress-regulating systems, stress-relevant brain regions and their interplay in patients with PTSD and BPD, to better explain the evolvement of clinical symptoms, such as affect dysregulation and dissociation that characterize both disorders. As a secondary aim, the current project focusses on the role of childhood trauma (CT), as a mutual environmental factor and possible cause of overlapping symptoms and characteristics in PTSD and BPD.

Both disorders are associated with exposure to traumatic events. Traumatic events, such as physical and sexual childhood abuse, in the early phase of development especially increase the risk of developing a psychiatric disorder, among them PTSD and BPD. The organism is especially sensitive to environmental influences in the early period of ontogeny, and changes of stress-regulating systems and stress-relevant brain regions occur in response to stressful environments. Therefore, research has focused on stress-regulating systems and stress-relevant brain regions in both disorders. Especially, the hypothalamic-pituitary-adrenal (HPA) axis, the sympathetic nervous system (SNS), fronto-limbic networks and the influences of glucocorticoids on memory retrieval and its neural activity have been investigated. Results suggest that some common features in patients with PTSD and BPD may be related to CT, in addition to distinct features that are related to e.g. genetics or single-event trauma. However, there has been little systematic investigation of distinct and overlapping features in PTSD and BPD, or of how CT is related to features that are present in both patient groups. To further characterize distinct and overlapping features in PTSD and BPD, and the role of CT, the following research questions are examined:

1. How do female patients with PTSD differ in their physiological and subjectively perceived stress response to an acute psychosocial stressor, compared with healthy women, and how do these differences relate to CT?
2. How does amygdala and hippocampus resting state functional connectivity (RSFC) differ between female patients with PTSD and BPD and healthy women, in a placebo condition and after hydrocortisone administration, and how does amygdala or hippocampus RSFC in the placebo or hydrocortisone condition relate to CT?

3. How do female patients with PTSD and BPD differ from healthy women in their neural activity during autobiographical memory (AM) retrieval after hydrocortisone administration compared with a placebo condition, and how do these differences relate to CT?

To investigate the psychosocial stress response, we used the Trier Social Stress Test, a well-established psychosocial stressor. To examine the effect of hydrocortisone on RSFC and on neural activity during AM retrieval, we used a standardized resting state scan and an autobiographical memory task adapted for functional magnet resonance imaging.

The main results of this dissertation are as follows. First, female patients with PTSD are characterized by a blunted cortisol response to a psychosocial stressor compared with healthy women. Measure of cortisol changes over time in response to a psychosocial stressor correlated negatively with severity of CT. We found no evidence for increased SNS reactivity in female patients with PTSD. Secondly, hippocampus dorsomedial prefrontal cortex (dmPFC) RSFC is reduced in female patients with PTSD and BPD. Hippocampus dmPFC RSFC correlated negatively with severity of CT and clinical symptoms. There were no differences between female patients and healthy women in amygdala RSFC. In addition, there was no influence of hydrocortisone on either amygdala or hippocampus RSFC, nor an interaction of hydrocortisone with group. Thirdly, female PTSD and BPD patients and healthy women did not differ in their neural activity during AM retrieval, neither in the placebo condition nor after hydrocortisone administration. Severity of CT correlated with a hydrocortisone induced pattern of neural activity. To conclude, the conducted studies extend findings on the physiological stress response and fronto-limbic network functioning and on the influence of glucocorticoids on memory retrieval and neural activity in patients with PTSD and BPD. Particularly, the revealed association of CT with a blunted cortisol stress response, decreased hippocampus dmPFC RSFC and a hydrocortisone induced neural activity pattern during AM retrieval, suggest an influence of CT on overlapping features in PTSD and BPD. This dissertation project condenses the current findings into a model that describes how CT might induce changes that partially account for overlapping features in PTSD and BPD. The model focusses on glucocorticoid receptor (GR) functioning and its consequences on HPA axis, SNS and fronto-limbic network functioning, and on the influence of glucocorticoids on memory retrieval and its associated neural activity. The current dissertation project yields important new insights into how CT as a common environmental factor in both disorders results in changes in stress-regulating systems and stress-relevant brain regions, and how these explain overlapping symptoms in both disorders.

Deutsche Zusammenfassung (German summary)

Epidemiologische Studien weisen auf hohe Komorbiditätsraten zwischen der Posttraumatischen Belastungsstörung (PTBS) und der Borderline Persönlichkeitsstörung (BPS) hin. Das Funktionsniveau von Patienten und Patientinnen, die unter beiden Störungen leiden, ist besonders eingeschränkt und der damit einhergehende Leidensdruck besonders hoch. Daher scheint die Untersuchung von gemeinsamen physiologischen und behavioralen Veränderungen und deren Ursache besonders erforderlich. Im vorliegenden Dissertationsprojekt sollen Merkmale stressregulierender Systeme, verwandter Hirnregionen sowie deren Interaktion in beiden Störungsgruppen untersucht werden um die Entstehung von Symptomen, wie einer defizitären Emotionsregulation und Dissoziationen, besser erklären zu können. Ein besonderer Fokus liegt hierbei auf Merkmalen, die beiden Störungen gemeinsam sind. Weiterhin soll die Rolle früher traumatischer Erfahrungen als gemeinsamer Umweltfaktor und mögliche Ursache für Merkmalen, die beide Störung aufweisen, untersucht werden.

Beide Störungen weisen eine hohe Prävalenz an traumatischen Erfahrungen auf. Vor allem traumatische Erfahrungen in der Kindheit führen zu einer erhöhten Vulnerabilität für psychische Störungen, eingeschlossen PTBS und BPS. Der Organismus ist vor allem zu Beginn der Entwicklung empfindlich für Umwelteinflüsse und es kommt zu Veränderungen von stressregulierenden Systemen und den dazugehörigen Hirnregionen auf Grund von belastenden Umweltfaktoren. Bisherige Studien untersuchten daher vor allem stressregulierende Systeme und die dazugehörigen Hirnregionen in Patienten und Patientinnen mit PTBS und BPS und in Probanden und Probandinnen mit traumatischen Kindheitserfahrungen. Vor allem die Funktionsweise der Hypothalamus-Hypophysen-Nebennierenrinden Achse (HHNA), dem sympathischen Nervensystem (SNS), fronto-limbischen Netzwerken und dem Einfluss von Glukokortikoiden auf den Gedächtnisabruf und die neuronale Aktivität wurden untersucht. Ähnliche Merkmale in beiden Störungsgruppen und bei Probanden und Probandinnen mit traumatischen Kindheitserfahrungen deuten auf gemeinsame ätiologische Mechanismen im Zusammenhang mit frühen traumatischen Lebensereignissen hin. Unterschiede zwischen den beiden Störungsbildern sind womöglich auf genetische Faktoren oder traumatische Erfahrungen im Erwachsenenalter zurückzuführen. Wie jedoch frühe traumatische Lebensereignisse zu den physiologischen Veränderungen beider Störungsgruppen führen und wie diese mit überlappenden Symptomen beider Störungen zusammenhängen, ist bisher noch unzureichend untersucht. Daher sind die folgenden Fragestellungen zu untersuchen:

1. Wie ist die physiologische und subjektive Stressreaktion auf einen psychosozialen Stressor in Patientinnen mit PTBS im Vergleich zu gesunden Kontrollprobandinnen verändert und wie hängt dieses mit traumatischen Kindheitserfahrungen zusammen?
2. Wie ist die funktionale Konnektivität von Amygdala und Hippocampus bei Patientinnen mit PTBS und BPS nach einer Verabreichung von Hydrokortison und nach der Verabreichung eines Placebos im Vergleich zu gesunden Kontrollprobandinnen verändert und gibt es einen Zusammenhang zwischen der Konnektivität in einer der beiden Bedingungen und traumatischen Kindheitserfahrungen?
3. Wie unterscheiden sich Patientinnen mit PTBS und BPS in der neuronalen Aktivität während des autobiographischen Gedächtnisabrufes von gesunden Kontrollprobandinnen nach einer Verabreichung von Hydrokortison und im Vergleich zu einer Placebo Bedingung und wie hängen diese Unterschiede mit traumatischen Kindheitserfahrungen zusammen?

Die psychosoziale Stressreaktion wurde mit dem Trier Social Stress Test, einem gut-etablierten psychosozialen Stresstest untersucht. Die funktionale Konnektivität und die neuronale Aktivität des autobiographischen Gedächtnisabrufes wurden mit einer Ruhemessung (resting state) und einem autobiographischen Gedächtnistest für funktionale Magnetresonanztomographie untersucht.

Die Durchführung des Dissertationsprojekts führte zu folgenden Ergebnissen: Erstens, Patientinnen mit PTBS zeigten eine reduzierte Kortisolreaktion auf einen psychosozialen Stressor im Vergleich zu gesunden Kontrollprobandinnen. Die Stärke der Kortisolreaktion nach psychosozialem Stress korrelierte negativ mit der Schwere früher traumatischer Lebensereignisse. Es konnte kein Hinweis auf eine erhöhte Reaktion des SNS gefunden werden. Zweitens, die funktionale Konnektivität zwischen Hippocampus und dorsomedialen präfrontalem Kortex ist in Patientinnen mit PTBS und BPS reduziert und korreliert negativ mit der Schwere früher traumatischer Lebensereignisse und der Symptomatik. Es zeigte sich kein Unterschied in der funktionalen Konnektivität der Amygdala. Weiterhin zeigte sich kein Einfluss von Hydrokortison auf die funktionale Konnektivität beider Areale, noch interagierte Hydrokortison mit der Zugehörigkeit zu einer der drei Gruppen. Drittens, es zeigte sich kein Unterschied zwischen Patientinnen mit PTBS, BPS und gesunden Kontrollprobandinnen in der neuronalen Aktivität des autobiographischen Gedächtnisabrufes, weder während der Placebo Bedingung noch nach einer Verabreichung von Hydrokortison. Die Schwere früher traumatischer Lebensereignisse korrelierte jedoch positiv mit einer Hydrokortison-induzierten neuronalen Aktivität während des autobiographischen Gedächtnisabrufes. Zusammenfassend,

erweitern die durchgeführten Studien Befunde zu Veränderungen der HHNA, des SNS, der fronto-limbischen Netzwerke und zu dem Einfluss von Glukokortikoiden auf den Gedächtnisabruf und deren neuronale Aktivität in Patientinnen mit PTBS und BPS. Vor allem die beschriebenen Zusammenhänge von traumatischen Kindheitserfahrungen mit einer reduzierten Kortisolreaktion, einer verringerten funktionalen Konnektivität zwischen Hippocampus und dorsomedialen präfrontalen Kortex und einer Hydrokortison-induzierten neuronalen Aktivität während des autobiographischen Gedächtnisabrufes, weisen auf einen Einfluss von frühen traumatischen Erfahrungen auf überlappende Charakteristika in PTBS and BPS hin. Ein zusammenfassendes Model, welches die beschriebenen Ergebnisse im Sinne einer Reaktion stressregulierender Systeme und den dazugehörigen Hirnregionen auf frühe traumatische Lebensereignisse integriert, wird präsentiert. Dieses integrative Modell legt hierbei einen besonderen Fokus auf den Einfluss von frühen traumatischen Lebensereignissen auf die Funktionswiese des Glukokortikoidrezeptors (GR) und deren Folgen für die HHNA, das SNS, fronto-limbische Netzwerke und den Einfluss von Glukokortikoiden auf den Gedächtnisabruf in Patientinnen mit PTBS und BPS. Das vorliegende Dissertationsprojekt gibt daher neue Einsicht, wie frühe traumatische Lebensereignisse zu Unterschieden in stressregulierenden Systemen und den dazugehörigen Hirnregionen führen und schließlich überlappende Symptome in Patienten und Patientinnen mit PTBS und BPS erklären.

1. Theoretical and empirical background

One in four patients with posttraumatic stress disorder (PTSD) suffers from comorbid borderline personality disorder (BPD), and almost one third of patients with BPD are also diagnosed with PTSD (Pagura et al., 2010). Patients with both disorders report the highest likelihood of lifetime suicide attempts and the lowest mental health related quality of life (Pagura et al., 2010). Given the high likelihood of comorbid PTSD and BPD and the great burden on those affected, mutual biological and behavioural characteristics and their cause seem worthwhile investigating and might help improve identification, prevention, and intervention for both disorders. The current dissertation project aims at further describing overlapping and distinct alterations in stress-regulating systems, stress-relevant brain regions and their interplay in patients with PTSD and BPD to better explain the evolution of clinical symptoms that characterize both disorders. In addition, the current project focusses on the role of childhood trauma (CT), as a mutual environmental factor and possible cause of overlapping symptoms and characteristics in PTSD and BPD.

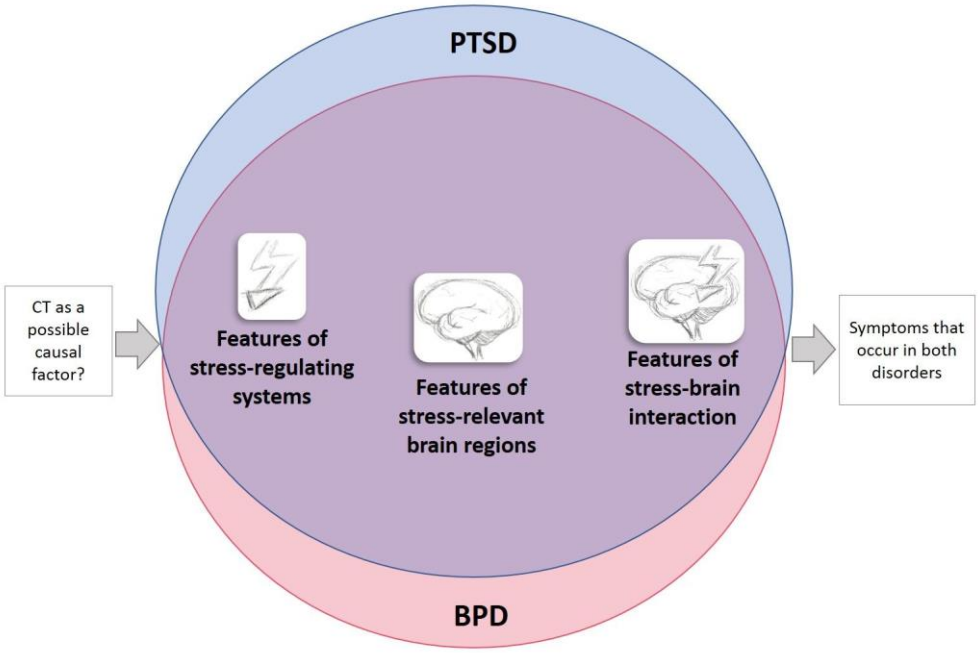
An association of both disorders with CT has been described (Beck et al., 2019; De Aquino Ferreira, Pereira, Benevides, & Melo, 2018; Gekker et al., 2018). A new nosological entity, complex PTSD, comprises symptoms of both disorders (Cloitre, Garvert, Brewin, Bryant, & Maercker, 2013) and is associated with repeated trauma especially in the early phase of development, e.g. physical and sexual childhood abuse (Cloitre et al., 2013). Given the high comorbidity and that CT is a mutual etiological factor, a new nosological entity seems reasonable and necessary. However, little is known about what symptoms are characteristic of both PTSD and BPD, which physiological alterations might explain these symptoms, and how CT as a mutual environmental factor might lead to those overlapping symptoms.

As the organism is especially sensitive to environmental influences in the early period of ontogeny, changes of stress-regulating systems and stress-relevant brain regions occur in response to highly stressful environments, e.g. trauma. Research has therefore focused on stress-regulating systems and stress-relevant brain regions in both disorders and in participants with CT. In particular, the hypothalamic-pituitary-adrenal (HPA) axis, the sympathetic nervous system (SNS), fronto-limbic networks and the influences of glucocorticoids on memory retrieval and its associated neural activity have been investigated.

However, a distinct group of PTSD patients report only symptoms of PTSD and no symptoms of BPD; this group has been described in association with single-event trauma (Cloitre et al., 2013). In addition, research has suggested biological differences in BPD patients with and without trauma (Goodman & Yehuda, 2002).

Taken together, these results suggest that there might be common features in both disorders which are possibly associated with CT and distinct features related to e.g. genetics or further environmental factors such as single-event trauma. Many studies focused either on one disorder or on environmental factors (e.g. CT). More research investigating overlapping features in different disorders, such as PTSD and BPD, is needed. The current dissertation project aims at further describing overlapping and distinct alterations in stress-regulating systems, stress-relevant brain regions and their interplay in patients with PTSD and BPD to better explain the evolution of clinical symptoms that characterize both disorders. As a secondary aim, the current project focusses on the role of CT as a possible causal factor explaining variance in overlapping symptoms and characteristics in PTSD and BPD (see figure 1).

Figure 1. The aim of the current dissertation project.



PTSD = Posttraumatic stress disorder, BPD = Borderline Personality disorder, CT = childhood trauma.

To do so, I describe diagnostic symptoms according to DSM criteria of the two disorders to reveal overlapping phenotypic changes in both disorders that might be associated with changes in stress-regulating systems, stress-relevant brain regions and their interplay. Subsequently, findings on the HPA axis and SNS activity and their relevance for mutual symptoms in patients with PTSD and BPD are reviewed in the introduction. In addition, I describe findings on stress-relevant brain regions, most importantly fronto-limbic networks, including the hippocampus, the amygdala and the prefrontal cortex (PFC) (Oitzl, Champagne, van der Veen, & de Kloet,

2010) and their influence on cognitive and affective processes in both disorders. I review the influence of glucocorticoids on memory retrieval processes and neural activity in both disorders to describe how stress-regulating systems and stress-relevant brain regions interact in patients with PTSD and BPD. In each of the above-named introductory chapters, the role of CT will be shortly addressed by highlighting findings that suggest an association of CT with overlapping features in PTSD and BPD. Lastly, I summarize the main findings of the existing body of literature and outline what still needs to be addressed to further characterize overlapping symptoms in PTSD and BPD and to understand how CT might lead to these alterations.

Before delving into these topics, one last remark should be kept in mind. The risk of developing a psychiatric disorder drastically increases in participants with CT (Heim & Nemeroff, 2001). Therefore, studies investigating the consequences of CT in healthy participants are rare. I describe whenever possible results on CT in healthy participants but often refer to results including participants irrespective of disease status. Importantly, results concerning CT will only be reported to further characterize overlapping features in PTSD and BPD. Results related to CT in other disorders, such as major depressive disorder (MDD) resulting in different phenotypes are beyond the scope of the current dissertation project and will only be reported to clarify the differentiation from PTSD and BPD.

1.1. Clinical symptoms of posttraumatic stress disorder (PTSD) and borderline personality disorder (BPD) and the role of childhood trauma (CT)

Starting from a more clinical perspective, which symptoms occurring in both PTSD and BPD are possibly explained by overlapping alterations in stress-regulating systems and stress-relevant brain regions? And are these overlapping symptoms possibly related to CT? To address these questions, I describe symptoms of each disorder (PTSD and BPD) separately, followed by a description of overlapping symptoms and their association with CT.

1.1.1. Clinical symptoms of PTSD

PTSD emerges after exposure to a severe traumatic event that provoked fear, helplessness, or horror. The disorder is mainly characterized by three symptoms: (1) re-experiencing unwanted images of the incident, dissociative reactions (e.g. flashbacks) and nightmares; (2) attempts to avoid reminders of the event, including persons and places and (3) hyperarousal resulting in physiological symptoms, such as insomnia, impaired concentration and hypervigilance. In addition, the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) emphasizes

negative self-worth, pathological blame, negative emotions and emotional numbness as symptoms of the disorder (American Psychiatric Association, 2013).

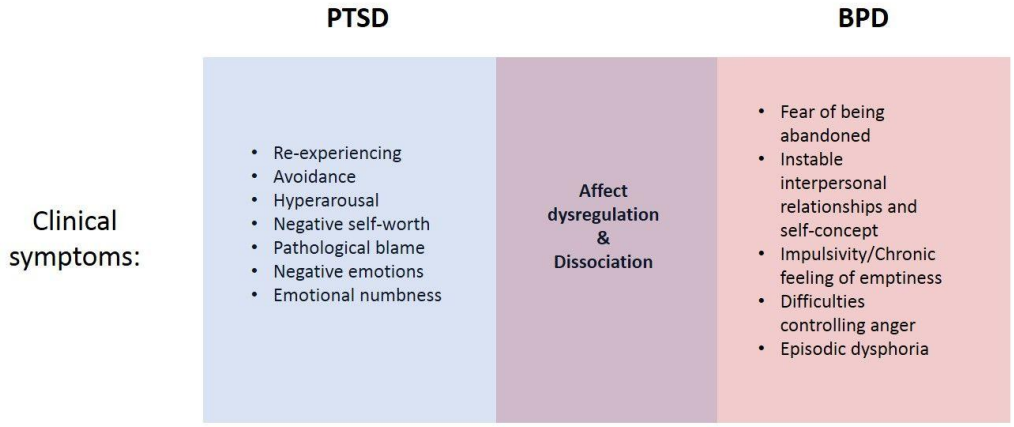
1.1.2. Clinical symptoms of BPD

BPD is characterized by an inflexible and long-lasting pattern of instability in interpersonal relationships, affect and self-concept and impulsivity affecting occupational and social situations. In particular the diagnostic criteria include: (1) fear of being abandoned, (2) pattern of instable interpersonal relationships, (3) instability of self-concept, (4) impulsivity including potential self-injuring domains, (5) suicidal acts, (6) affect instability including e.g. episodic dysphoria, (7) chronic feeling of emptiness, (8) difficulties controlling anger and (9) dissociative symptoms (American Psychiatric Association, 2013).

1.1.3. Overlapping symptoms of PTSD and BPD

In addition to several distinct symptoms, BPD and PTSD show a significant overlap in symptoms, such as dissociation (Barnow et al., 2012; Bremner et al., 1992) and affect dysregulation (Lanius, Frewen, Vermetten, & Yehuda, 2010; Van Dijke, 2012) (see figure 2), which are at the same time core features of complex PTSD (Ford & Courtois, 2014). Affect dysregulation refers to the inability to control or regulate emotional responses, including, for example, an inability to calm down, rapid mood changes and an inability to engage in goal-directed behaviour (Briere, Hodges, & Godbout, 2010). Consequences are transparently extensive, ranging from inability to control anger in occupational situations to excessive mistrust in relationships. Affect dysregulation has also been described as predicting subsequent dissociation (Powers, Cross, Fani, & Bradley, 2015). Dissociation, which aggravates in stressful and emotional situations (Paret, Hoesterey, Kleindienst, & Schmahl, 2016), refers to disruptions in the integration of memory and perception of self and environment (e.g. depersonalization, derealization) and contributes to further functional impairment (Powers et al., 2015).

Figure 2. Clinical symptoms in PTSD and BPD.



Schematic representation of overlapping symptoms in PTSD and BPD. PTSD = Posttraumatic Stress Disorder, BPD = Borderline Personality Disorder.

Taken together, affect dysregulation and dissociation are overlapping symptoms in both disorders and might be related to overlapping alterations in stress-regulating systems and stress-relevant brain regions. However, the question arises whether these symptoms are related to CT, as CT is one possible factor explaining alterations in stress-regulating systems and stress-relevant brain regions in both disorders.

1.1.4. The role of CT in overlapping symptoms of PTSD and BPD

Affect dysregulation and dissociation could indeed plausibly result from common etiological factors (Knefel, Tran, & Lueger-Schuster, 2016). An association of physical childhood abuse with dissociative symptoms in a randomly selected sample irrespective of disease status has been described (Mulder, Beautrais, Joyce, & Fergusson, 1998). In addition, a review summarizing studies on CT, affect dysregulation, and psychiatric co-morbidities suggested a relationship between CT and affect dysregulation (Dvir, Ford, Hill, & Frazier, 2014). Therefore, affect dysregulation and dissociation might be overlapping symptoms in both disorders that are related to CT. Understanding, acceptance and interpersonal regulation of emotions may be particularly problematic for individuals exposed to CT. This might lead to further distinct symptoms in both disorders depending on genetic variations and environmental factors such as trauma during adulthood in PTSD (Pratchett & Yehuda, 2011) and disorganized attachment interactions in BPD (Khoury et al., 2019).

Taken together, CT is associated with affect dysregulation and dissociation, which are also features of PTSD and BPD. Since affect dysregulation and dissociation are overlapping in PTSD and BPD and are related to CT, the following chapters aim to further investigate how overlapping feature of stress-regulating systems and stress-relevant brain regions might explain the emergence of these symptoms.

Previous studies have suggested an association between affect regulation (Het, Schoofs, Rohleder, & Wolf, 2012), dissociation (Simeon, Knutelska, Smith, Baker, & Hollander, 2007) and stress-regulating systems. Therefore, in the following I review findings on HPA axis and SNS activity in PTSD and BPD and their relation to CT.

1.2. Stress-regulating systems in PTSD and BPD and the role of CT

Before I describe stress reactivity in patients with PTSD and BPD, a brief outline of the stress response in healthy participants is presented.

The stress response is mainly characterized by two major stress systems, the HPA axis and the SNS, with cortisol and norepinephrine as their respective end-products. Appraisal of a stressful event starts a cascade which activates these two systems. This is mainly associated with activation in the PFC and limbic structures, in particular the amygdala and the hippocampus. The hypothalamus is connected to these brain regions and initiates a rapid response of the SNS and slower response of the HPA axis (Schwabe & Wolf, 2013).

The SNS stress response is characterized by a rapid release of noradrenaline and adrenaline (Hermans, Henckens, Joëls, & Fernández, 2014). Noradrenaline is primarily released in the locus coeruleus (LC) as well as by brainstem sites. This is followed by a peripheral release of adrenaline from the adrenal medulla by activation of sympathetic pathways that project indirectly to the end organs and the adrenal medulla (Valentino & Van Bockstaele, 2008).

Second, a slower release of glucocorticoids via the HPA axis takes place (Hermans et al., 2014). The corticotropin-releasing hormone (CRH) is released from the hypothalamus stimulating the secretion of adrenocorticotrophic hormone (ACTH) from the pituitary. ACTH increases the synthesis and release of glucocorticoids from the adrenal cortex. Glucocorticoids then bind at two different nuclear receptors in the brain, firstly with higher affinity at the mineralocorticoids receptor (MR) also known as Type II or NR3C2, which is mainly distributed in limbic structures, and then with lower affinity at the glucocorticoid receptor (GR) also known as Type I or NR3C1, which is distributed across the whole brain (De Kloet, 2014). Additionally, glucocorticoids initiate a negative feedback loop predominantly via GR targeting the pituitary, hypothalamus, and hippocampus, thus regulating HPA axis activation and an adaptive stress response (De Kloet, Joëls, & Holsboer, 2005).

The HPA axis and SNS also influence each other. Since the main source of norepinephrine in the central nervous system is the LC and the LC receives excitatory CRH inputs from different regions, among them the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus, interaction of the HPA axis and the SNS takes place at the level

of CRH (Jedema & Grace, 2004). Accordingly, CRH projecting neurons from the amygdala enhance firing rate of neurons in the LC resulting in an increased noradrenaline release (McCall et al., 2015). In line with these results, adrenalectomized rats show increased CRH release and increased LC firing (Pavcovich & Valentino, 1997). However, cortisol treatment prevented this increase, indicating that feedback inhibition by glucocorticoids may results in a decreased responses of the LC and reduced noradrenaline release (Kvetnanský et al., 1993). In turn, the adrenergic system stimulates CRH release at hypothalamic level by norepinephrines (Fehm, Voigt, Lang, & Pfeiffer, 1980; Weiner & Ganong, 1978).

In addition to basal HPA axis and SNS activity, usually investigated by extraction of unstimulated blood, saliva or urine samples, studies investigated stimulated HPA axis and SNS activity in patients with PTSD and BPD and in participants with CT. For this purpose, different tasks and stressors have been used. A frequently used psychosocial stressor, is the Trier Social Stress Test (TSST) (Kirschbaum, Pirke, & Hellhammer, 1993) (for detailed description see chapter 2.2.2). Other studies used cognitive challenge tests, including e.g. challenging arithmetic and Stroop tasks (Bremner et al., 2003; Gotthardt et al., 1995) or the cold pressor test, in which participants immerse their hands in ice cold water for a few minutes, and which induces most notably profound SNS activation (Giesbrecht, Smeets, & Merckelbach, 2008; Lovallo, 1975; Santa Ana et al., 2006). In PTSD patients many studies used trauma-related stimuli to evoke a stress reaction, e.g. reading and imagination of personalized trauma scripts or audiotapes of combat sounds in veterans (Elzinga, Schmahl, Vermetten, van Dyck, & Bremner, 2003; Liberzon, Abelson, Flagel, Raz, & Young, 1999).

To investigate HPA axis feedback-regulation, the dexamethasone suppression test is frequently used. In the dexamethasone suppression test, usually 1 mg of dexamethasone is administered orally and cortisol levels are measured the following day. Increased cortisol values indicate a failure to suppress cortisol and is considered evidence for HPA axis hyperactivity and attenuated feedback regulation (Coryell & Schlesser, 2001). GR expression and sensitivity have also been investigated as markers of HPA axis feedback-regulation. Central GR sensitivity measurement is only possible postmortem. There are yet no studies investigating central GR expression (e.g. in the hippocampus) in human patients with PTSD or BPD. Therefore, the majority of studies investigated GR sensitivity in peripheral blood.

In the following chapters, I will describe findings on (1) basal SNS activity, followed by findings on (2) stimulated activity of the SNS, followed by findings on (3) basal HPA axis activity and lastly findings on (4) stimulated activity of the HPA axis in both disorders and in participants with CT. Findings on stimulated activity include various studies using different

stressors. Findings on trauma-related stressors are mainly presented in patients with PTSD, while the cognitive challenge test, cold pressor test and TSST are more commonly used in patients with BPD.

1.2.1. Stress-regulating systems in PTSD

Results concerning SNS activity in patients with PTSD hint towards increased basal and stimulated SNS activity. Meta-analysis of basal catecholamine in plasma and urine revealed increased catecholamines in patients with PTSD (Pan, Kaminga, Wen, & Liu, 2018), and similar results for 24-hour urine have been reported (Wingenfeld, Whooley, Neylan, Otte, & Cohen, 2015). In addition, studies revealed higher heart rate (Buckley, Holohan, Greif, Bedard, & Suvak, 2004; Paulus, Argo, & Egge, 2013) and blood pressure (Muraoka, Carlson, & Chemtob, 1998; Paulus et al., 2013) in patients with PTSD. Concerning stimulated SNS activity, an increased norepinephrine response (Geracioti et al., 2008) and exaggerated responses in skin conductance, heart rate and epinephrine were shown in response to trauma-related stimuli (Liberzon et al., 1999). SNS reactivity to a psychosocial stressor revealed no differences concerning blood pressure and heart rate (MacMillan et al., 2009; Zaba et al., 2015). However, a subgroup of patients with PTSD characterized by a low cortisol response showed higher heart rate in response to the stressor (Zaba et al., 2015). Results hint at differences in SNS reactivity to trauma-related versus psychosocial stress induction. Since the majority of studies used trauma-related stimuli, future studies using psychosocial stressors are needed.

Regarding the HPA axis, basal cortisol levels tend to be lower in patients with PTSD compared with healthy participants (Meewisse, Reitsma, de Vries, Gersons, & Olff, 2007; Morris, Compas, & Garber, 2012). Studies investigating stimulated HPA axis activity revealed differences between studies using trauma-related stimuli and psychosocial stress induction. Studies using trauma-related stimuli showed increased cortisol reactivity (De Kloet et al., 2006; Elzinga et al., 2003). Studies using psychosocial stressors or cold pressor tests described a blunted cortisol response in patients with PTSD (Santa Ana et al., 2006; Wichmann, Kirschbaum, Bohme, & Petrowski, 2017; Zaba et al., 2015). Therefore, there is preliminary evidence of blunted cortisol reactivity to non-traumatic stress in patients with PTSD.

GR expression and sensitivity and HPA axis feedback sensitivity have been additionally investigated in patients with PTSD. These studies show an increased glucocorticoid sensitivity in peripheral blood cells (Szeszko, Lehrner, & Yehuda, 2018; Yehuda, Golier, Yang, & Tischler, 2004). In line with these results, enhanced feedback sensitivity of the HPA axis using the dexamethasone test in patients with PTSD was revealed (Yehuda et al., 1993). It has been

suggested that blunted basal and stress induced cortisol release could be a consequence of enhanced GR binding in peripheral blood (Labonte, Azoulay, Yerko, Turecki, & Brunet, 2014). In addition, blunted cortisol levels might contribute to increased catecholamine output due to missing inhibitory effects of glucocorticoids on CRH release and therefore adrenergic system activation in patients with PTSD (see chapter 1.2. for further details on interaction of CRH and adrenergic system) (Zoladz & Diamond, 2013).

But how does stress reactivity in PTSD relate to symptoms of PTSD? Reexperiencing and hyperarousal symptoms have been described as the result of failed inhibitory control over fear-induced arousal (Frewen & Lanius, 2006). High SNS activity might therefore be related to symptoms of hyperarousal. Another study showed descriptively higher dissociation severity in cortisol non-responders in PTSD patients (Wichmann et al., 2017).

Taken together, lower basal and stimulated (psychosocial stress induction) cortisol and high resting SNS activity seem to characterize PTSD. Higher SNS activity and low cortisol in turn might be related to dissociation and increased arousal in patients with PTSD. As most studies used trauma-related stimuli, the investigation of the stress response to a psychosocial stressor gained less attention. Therefore, this dissertation project aims at investigating the physiological stress response in addition to the subjectively perceived stress response and dissociation in response to a psychosocial stressor in patients with PTSD. CT will be considered as a factor explaining variance in the stress response.

1.2.2. Stress-regulating systems in BPD

With regard to basal SNS activity, the majority of studies hint towards increased activity in patients with BPD, which is in line with results in patients with PTSD. Patients with BPD showed lower heart rate variability (HRV), indicating higher sympathetic activation (Koenig, Kemp, Feeling, Thayer, & Kaess, 2016; Weinberg, Klonsky, & Hajcak, 2009). In addition, higher baseline heart rate (Eddie et al., 2018) and elevated blood pressure in association with BPD have also been shown (Barber, Ringwald, Wright, & Manuck, 2019; Wingenfeld et al., 2015). However, evidence for lower blood pressure or no differences in blood pressure have also been found (Duesenberg et al., 2019; Wingenfeld et al., 2018). Concerning SNS reactivity, results are contradictory. Several studies showed a blunted salivary alpha amylase (sAA), heart-rate and blood pressure response after psychosocial stress induction (Aleknaviciute et al., 2016; Nater et al., 2010; Wingenfeld et al., 2018). Nevertheless, there are also studies describing no differences (Inoue et al., 2015; Simeon et al., 2007) or increased sAA reactivity in response to stress in patients with BPD (Ehrenthal, Levy, Scott, & Granger, 2018). Since trauma-related

stressors are uncommon in studies investigating stress reactivity in BPD, it is impossible to compare findings in BPD to findings in PTSD.

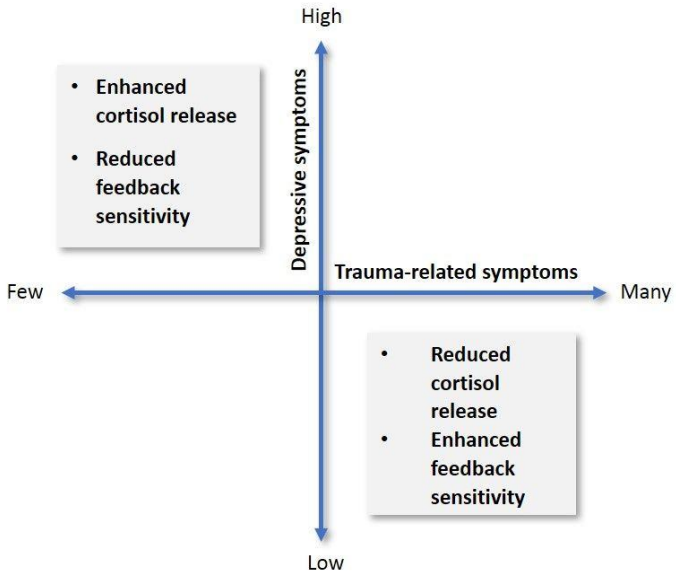
Concerning basal HPA axis activity, studies have shown enhanced basal cortisol release in patients with BPD (Drews, Fertuck, Koenig, Kaess, & Arntz, 2019; Wingenfeld, Spitzer, Rullkötter, & Löwe, 2010; Zimmerman & Choi-Kain, 2009). Comorbid depressive symptoms and PTSD seem to strongly influence these results, with low cortisol in PTSD and increased cortisol in MDD (Wingenfeld, et al., 2010). Concerning HPA axis reactivity, we found, similar to patients with PTSD, a blunted cortisol release in response to a psychosocial stressor (Duesenberg et al., 2019). This is line with former studies reporting a blunted cortisol response (Deckers et al., 2015; Drews et al., 2019; Ehrenthal et al., 2018; Nater et al., 2010). However, a higher cortisol response in patients with BPD, and especially in those with high dissociation has also been shown (Simeon et al., 2007). Again, as trauma-related stressors are uncommon in studies investigating stress reactivity in BPD, no comparison to findings in PTSD is possible.

Peripheral GR sensitivity appears to be under-investigated in patients with BPD, compared with findings in PTSD. There is some evidence for reduced GR expression and sensitivity (Martín-Blanco et al., 2014) and reduced feedback regulation of the HPA axis (Wingenfeld et al., 2010) in this patient group. However, enhanced sensitivity to glucocorticoids has also been proposed in patients with BPD (Wingenfeld et al., 2013; Wingenfeld & Wolf, 2015). Existing literature suggests two different subtypes of BPD. One subtype is characterized by trauma-related symptoms with decreased to normal cortisol release and enhanced feedback sensitivity. The second proposed subtype is characterized by depression-related symptoms with enhanced cortisol release and reduced feedback sensitivity similar to findings in depressed patients (Wingenfeld, et al., 2010) (see figure 3). For the current dissertation project, the first proposed subtype, which is mainly characterized by trauma-related symptoms with decreased cortisol response and enhanced feedback sensitivity, is of particular interest.

But how does stress reactivity in BPD relate to symptoms of BPD? One study described a higher subjective perceived stress response coupled with substantial cortisol and alpha-amylase (AA) hypo-reactivity in patients with BPD (Nater et al., 2010). In addition, authors of a meta-analysis proposed that lower parasympathetic activation might explain difficulties in emotion regulation and impulsivity (Koenig et al., 2016). High basal SNS activity and low norepinephrine and cortisol stress reactivity might be related to increased negative mood and dissociation after exposure to a stressor. However, contradicting results have also been found (Simeon et al., 2007).

Taken together, results concerning SNS mainly point towards increased basal and stimulated activity in patients with BPD. Attenuated cortisol reactivity has additionally been shown. This might be related to increased negative mood and dissociation. Basal cortisol release and feedback sensitivity mainly depend on the subtype of BPD (see figure 3).

Figure 3. Psychopathology of BPD and HPA axis dysregulation

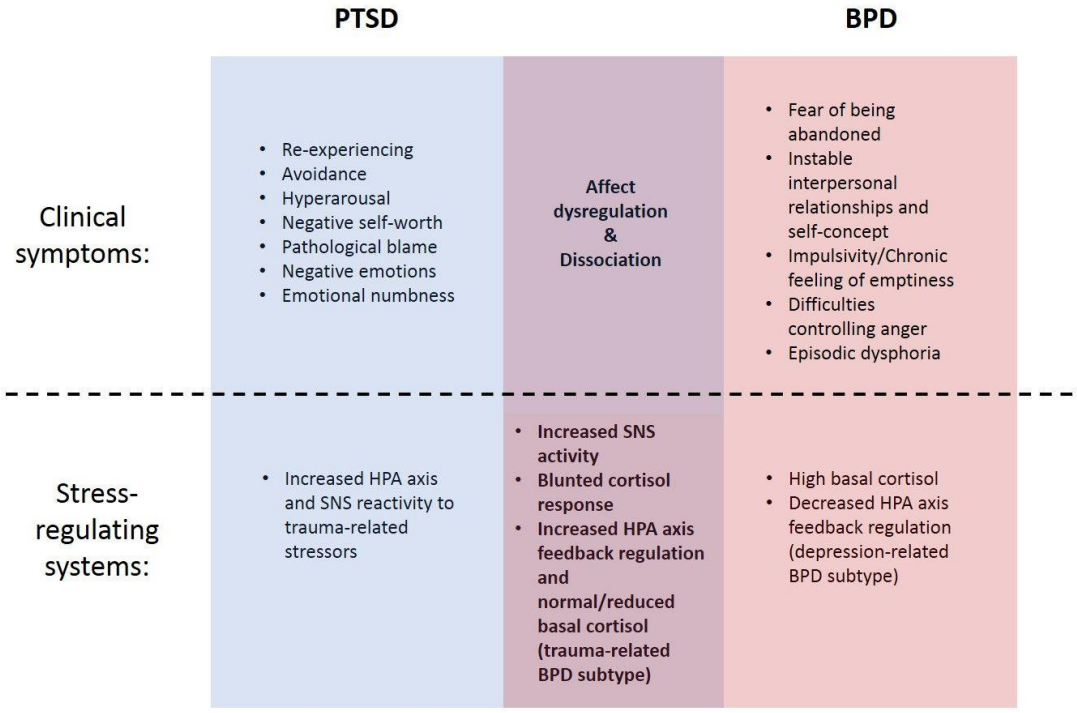


Psychopathology of BPD in two possible dimensions related to depressive symptoms and trauma-related symptoms according to (Katja Wingenfeld, Spitzer, Rullkötter, et al., 2010).

1.2.3. Overlapping features of PTSD and BPD in stress-regulating systems

In summary, blunted stimulated cortisol activity and high resting SNS activity are consistent results in both patient groups (see figure 4). HPA axis feedback regulation and basal cortisol release in patients with BPD, however, might depend on the subtype of BPD (see figure 3).

Figure 4. Clinical symptoms and stress-regulating systems in PTSD and BPD.



Schematic representation of overlapping symptoms and characteristics of HPA axis, SNS and HPA axis feedback regulation in patients with PTSD and BPD. PTSD = Posttraumatic stress disorder, BPD = Borderline Personality disorder, SNS = Sympathetic nervous system, HPA axis = Hypothalamic-pituitary-adrenal axis.

The question arises: which factors lead to decreased stimulated cortisol activity and high basal SNS activity as overlapping features in PTSD and BPD, possibly explaining symptoms such as dissociation and hyperarousal? CT as a possible factor will be reviewed in the next chapter.

1.2.4. The role of CT in overlapping features of PTSD and BPD in stress-regulating systems

What do we know about changes in the HPA axis and SNS in participants with CT? Concerning the SNS, results hint towards higher basal and stimulated SNS activity, in line with results described in patients with PTSD and BPD. Higher blood pressure in healthy participants with CT (Su et al., 2015) and higher heart rate in patients with PTSD related to childhood abuse have been shown (Bremner et al., 2003). In addition, increased sAA response to stress in relation to CT in healthy participants has also been reported (Kuras et al., 2017). Film clips displaying officers in highly stressful incidents resulted in increased catecholamine response in participants with CT with no current axis I disorder (Otte et al., 2005). However, a significant negative correlation between sAA release in response to a psychosocial stressor and severity of CT has been described in patients with BPD (Duesenberg et al., 2019). Again, studies using

trauma-related stimuli are common while psychosocial stress induction is less well examined in studies investigating CT.

Concerning HPA axis functioning in participants with CT, most studies hint towards blunted basal and stimulated activity, similar to the findings described in PTSD and BPD. CT was related to blunted basal cortisol in healthy participants with CT (Kuras et al., 2017) and in patients with personality disorders (Flory et al., 2009). However, a recent meta-analysis of studies investigating CT in healthy individuals showed no differences in basal cortisol (Fogelman & Canli, 2018). Furthermore, an attenuated cortisol response to psychosocial stress was associated with CT in females without PTSD and BPD (Carpenter, Shattuck, Tyrka, Geracioti, & Price, 2011; MacMillan et al., 2009; Pierrehumbert et al., 2009) and in patients with BPD (Duesenberg et al., 2019) However, others revealed no differences in stimulated cortisol activity (Bremner et al., 2003; Fogelman & Canli, 2018) or a higher cortisol response to psychosocial stress in participants with CT (Heim et al., 2000). Since this effect of a higher cortisol response was particularly robust in women with current depressive symptoms, factors such as comorbid mood disorders seem to influence these results.

An influence of CT on central GR downregulation has been proposed (McGowan et al., 2009). This in turn changes the sensitivity of stress regulating systems to the inhibitory effects of glucocorticoids, leading to increased CRH production with increased HPA axis responses to stress (Heim et al., 2000; Meaney et al., 1996). These results suggest that central GR expression and binding might be reduced in participants with CT and might explain features of HPA axis and SNS. Initial results suggest decreased GR expression in peripheral blood in patients with BPD (Martín-Blanco et al., 2014), however increased GR expression in peripheral blood has been shown in veterans with PTSD (Szeszko et al., 2018; Yehuda et al., 2004). These findings suggest heterogeneous results concerning peripheral GR expression and sensitivity. GR sensitivity might differ between patients with PTSD and BPD due to trauma during adulthood and participants with CT. In addition, differences in the central nervous system (CNS) and peripheral blood might explain diverging results. However, these effects seem to be under-investigated and further studies are needed.

In summary, blunted stimulated cortisol activity and a high resting SNS activity are consistent findings in both patient groups and might be related to CT (see figure 4). HPA axis feedback regulation and basal cortisol release in patients with BPD, however, might depend on the subtype of BPD (see figure 3).

As alterations in stress-regulating systems have been shown and these seem to be highly influenced by stress-relevant brain regions, alterations of stress-relevant brain regions in both

disorders might help explain symptoms such as affect dysregulation and dissociation. In addition, stress has damaging effects on the brain (Wingenfeld et al., 2010), especially during development (Lupien, McEwen, Gunnar, & Heim, 2009). Changes induced by CT are, therefore, likely to additionally involve stress-relevant brain regions, most importantly the hippocampus, the amygdala and the PFC (Oitzl et al., 2010). Therefore, in the following pages, I summarize findings on stress-relevant brain regions and their influence on cognitive and affective processes in both disorders and their association with CT.

1.3. Stress-relevant brain regions in PTSD and BPD and the role of CT

Since evidence suggests that chronic or repeated stress has damaging effects on the brain, a large body of research over the past few decades has made use of neuroimaging methods to investigate stress-associated disorders as PTSD and BPD. One technique that is often used to investigate neural activity is functional magnet resonance imaging (fMRI). FMRI makes use of the magnetic properties of haemoglobin and changes in oxygen concentration in the brain (Blood Oxygen Level Dependent (BOLD)). Inferences on neural activity can be indirectly drawn from the measured BOLD contrast (i.e. comparison of BOLD signal between conditions), based on the assumption that more active neurones have higher oxygen consumption (Dogil et al., 2002). In particular, neural activity during various affective and cognitive tasks in both patients with disorders and participants with CT have been investigated using this method. Many studies have also used resting state functional connectivity (RSFC), a method which compares the similarities of the BOLD signals from different brain regions to analyze which brain regions are co-activated and are, thus, functionally related to each other (Bijsterbosch, Smith, & Beckmann, 2017). However, heterogeneity among tasks is high and there is a lack of studies investigating neural activity during the same task in different disorders. In addition, the pattern or direction of change in RSFC in relation to different etiological factors and disorders is often inconsistent. Different processing steps for motion correction might influence direction of results and contribute to inconsistent findings (Marusak et al., 2016). Therefore, there is a need for studies investigating RSFC and task related activation in the same design across different patient groups. The current dissertation aims at investigating these issues in patients with PTSD and BPD.

The hippocampus, the amygdala, and the PFC particularly interact to control stress-regulating systems and emotional processes (Oitzl et al., 2010). Psychiatric research has therefore focused on the amygdala, a brain region mainly associated with fear conditioning (LeDoux, 2007) and the hippocampus, a brain region which has been most strongly implicated

in learning and memory (Sapolsky, 2000). The PFC, involved in planning and cognitive control of actions and thoughts (Miller & Cohen, 2001), is a further brain area of interest for the etiology of different disorders. RSFC between limbic and prefrontal regions has also been addressed (Marusak et al., 2016).

Therefore, in the following I review findings revealing changes in these brain areas, starting with findings on (1) RSFC and followed by findings on (2) neural activity during various tasks in patients with PTSD and BPD and in participants with CT.

1.3.1. Stress-relevant brain regions in PTSD

Results concerning RSFC in patients with PTSD hint towards a less functionally connected hippocampus, increased amygdala anterior cingulate cortex (ACC) RSFC and decreased inhibition of the amygdala by the medial prefrontal cortex (mPFC). At a more detailed level, decreased hippocampus RSFC with the default mode network (Chen & Etkin, 2013) and decreased inhibition of amygdala by the mPFC and hippocampus (Shin, Rauch, & Pitman, 2006) have been demonstrated. This is in line with the smaller hippocampal volumes that have consistently been shown in PTSD (O'Doherty, Chitty, Saddiqui, Bennett, & Lagopoulos, 2015; Pavić et al., 2007; Shin et al., 2006; Weniger, Lange, Sachsse, & Irle, 2009). Another study revealed decreased amygdala ventromedial PFC (vmPFC) RSFC (Stevens et al., 2013). Furthermore, stronger positive functional coupling between the amygdala and dorsomedial prefrontal cortex (dmPFC) and ACC (Brown et al., 2014) have been shown. Increased amygdala connectivity with the ACC might represent enhanced fear-related memory encoding in healthy participants (Hakamata et al., 2020). Therefore, an overactive amygdala with increased RSFC to ACC could explain processes such as increased attentional bias to fearful stimuli (El Khoury-Malhame et al., 2011) and fear-generalization (Morey et al., 2015).

Results regarding neural activity during different tasks suggest increased amygdala activation in patients with PTSD. Results for hippocampus and PFC regions have been more heterogeneous, with most studies describing lesser activation. In detail, amygdala activation during symptomatic states and in response to trauma-related stimuli was increased, while the PFC has been shown to be hyporesponsive in patients with PTSD (Shin et al., 2006). Another study suggested that amygdala activation and ACC habituation after trauma are predictive of development of PTSD symptoms (Stevens et al., 2017). Results concerning hippocampus associative learning showed higher (Brohawn, Offringa, Pfaff, Hughes, & Shin, 2010) and lesser activation (Bremner et al., 2003). A recent review, however, suggests that deficits due to decreased hippocampal function and connectivity in associative-learning is a risk factor for

PTSD development (Lambert & McLaughlin, 2019). Decreased hippocampus activation has been associated with memory deficits described in PTSD, including semantic memory and autobiographical memory (AM) retrieval (Wingenfeld et al., 2012). Diminished PFC activation has been associated with an impairment in attentional control (Rauch, Shin, & Phelps, 2006), working memory performance (McDermott et al., 2016), cognitive inhibition (Clausen et al., 2017) and AM and semantic memory performance (Wingenfeld et al., 2012).

Taken together, findings suggest that the combination of hypo-responsive prefrontal brain areas, an overactive amygdala with increased ACC and decreased PFC RSFC, and a less active and smaller hippocampus characterize patients with PTSD. This might result in poor cognitive control and a low threshold for perceived salience.

1.3.2. Stress-relevant brain regions in BPD

Results in patients with BPD suggest increased RSFC of amygdala to insula, orbitofrontal cortex (OFC) and putamen and increased amygdala and hippocampus RSFC with ACC. In detail, patients with BPD exhibit stronger connectivity between the amygdala and a cluster comprising the insula, OFC, and putamen (Krause-Utz et al., 2014). In addition, high resting state activity in the left hippocampus and amygdala, with increased RSFC with the ACC was described in patients with BPD, suggesting that the amygdala is overactive at rest (Salvador et al., 2016). Studies investigating structural differences in patients with BPD described amygdala, hippocampus and ACC volume reduction in line with results on RSFC in these brain regions (Wingenfeld, et al., 2010). Hyperconnectivity of the amygdala might be related to affective hyperarousal (Salvador et al., 2016).

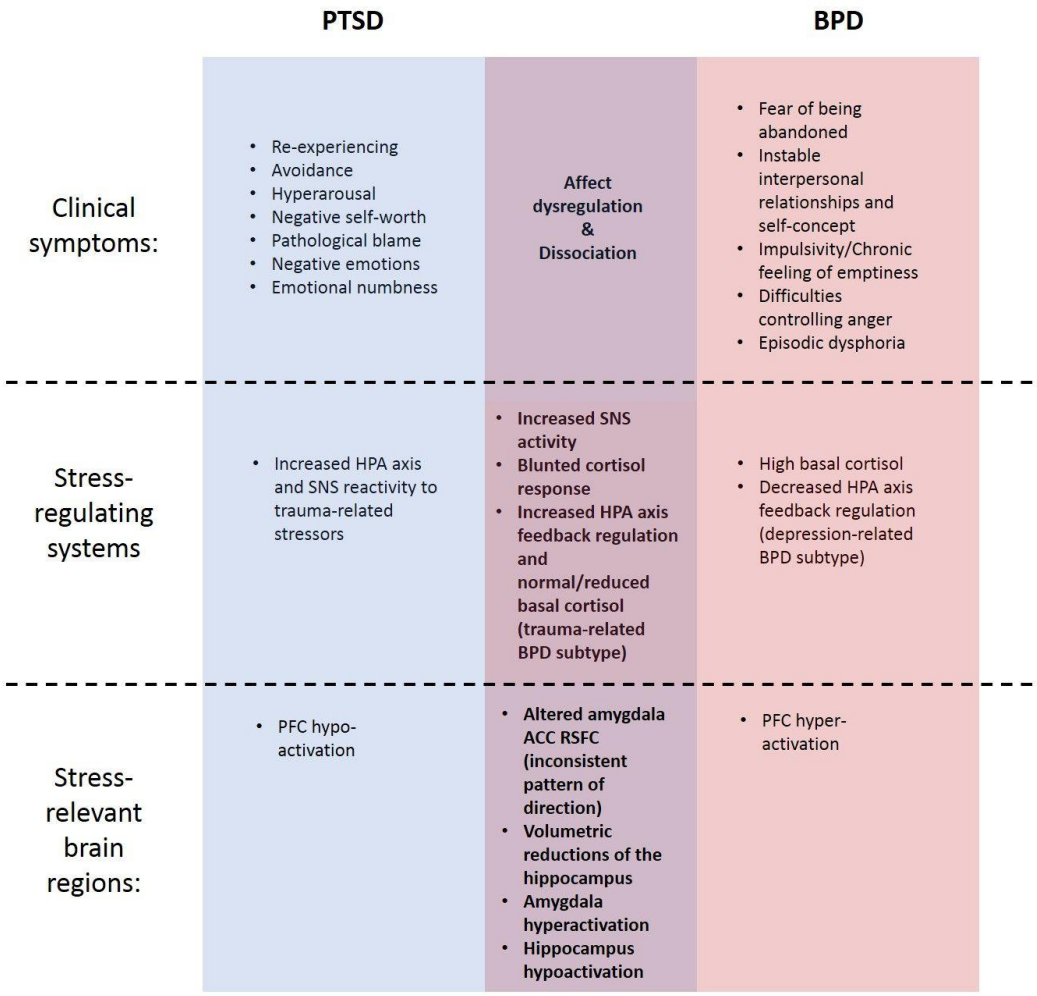
Concerning neural activity during various tasks, results hint towards amygdala hyperactivation and ACC and hippocampus hypoactivation. In detail, limbic hyperactivation similar to that of patients with PTSD has been shown in patients with BPD (Donegan et al., 2003; Schulze, Schulze, Renneberg, Schmahl, & Niedtfeld, 2019). A failure of activation of the ACC has been shown in patients with BPD, possibly further explaining affect dysregulation (Schmahl, Vermetten, Elzinga, & Bremner, 2004). Another positron emission tomography (PET) study reported PFC hypermetabolism and hippocampus hypometabolism (Juengling et al., 2003). Accordingly, prefrontal and hippocampus functioning might be related to cognitive deficits such as decreased AM retrieval, declarative memory retrieval (Wingenfeld et al., 2013), working memory performance (Stevens, Burkhardt, Hautzinger, Schwarz, & Unckel, 2004), executive control (Hagenhoff et al., 2013) and decreased explicit emotion regulation in patients with BPD (Schulze et al., 2011).

In summary, increased amygdala RSFC to ACC, OFC, insula and putamen, hyperactivation of the amygdala and ACC, and hippocampus hypoactivation characterize patients with BPD. This might partly explain the hyperarousal-affective dysregulation syndrome.

1.3.3. Overlapping features of PTSD and BPD in stress-relevant brain regions

The overlapping features that characterize both PTSD and BPD are amygdala hyperactivation, increased amygdala ACC RSFC, and hippocampus hypoactivation (see figure 5). Overlapping characteristics in both disorders might partially explain affect dysregulation. Consequently, the question arises whether the presence of CT might explain the overlap in amygdala hyperactivation, increased amygdala ACC RSFC and hippocampus hypoactivation?

Figure 5. Clinical symptoms, stress-regulating systems and stress-relevant brain regions in PTSD and BPD.



Schematic representation of overlapping symptoms and characteristics of HPA axis, SNS and HPA axis feedback regulation and neuroimaging findings in patients with PTSD and BPD. PTSD = Posttraumatic stress disorder, BPD = Borderline Personality disorder, SNS = Sympathetic nervous system, HPA axis = Hypothalamic-pituitary-adrenal axis, PFC = Prefrontal cortex, ACC = Anterior cingulate cortex, RSFC = Resting state functional connectivity.

1.3.4. The role of CT in overlapping features of PTSD and BPD in stress-relevant brain regions

Overlapping features of stress-relevant brain regions in both disorders are in line with results in participants with CT. A recent meta-analysis of studies examining amygdala RSFC in relation to internalizing symptoms or risk factors such as CT, irrespective of disease status, revealed changes in amygdala ACC RSFC (Marusak et al., 2016). However, results regarding the pattern of amygdala ACC RSFC were heterogeneous, with some studies reporting increased RSFC while others reported decreased RSFC (Marusak et al., 2016). Additionally, a hyperactive amygdala (McCrory et al., 2013) and a hypoactive (Lambert et al., 2017) and smaller hippocampus (Calem, Bromis, McGuire, Morgan, & Kempton, 2017) have been shown in participants with CT.

In summary, both disorders displayed altered amygdala ACC RSFC (with an inconsistent pattern of direction), amygdala hyperactivation, and a smaller and hypoactive hippocampus. These features are also related to CT. Given that overlapping features in stress-regulating systems and stress-relevant brain regions have been shown in both disorders, and furthermore, to be associated with CT, the question arises: how do stress-regulating systems and stress-relevant brain regions interact in patients with PTSD and BPD? Studies investigating these issues have been scarce until recently. In the following section, I review the existing literature concerning the influence of stress or glucocorticoids on RSFC and on cognitive processes and their associated neural activity, in patients with PTSD and BPD and in participants with CT.

1.4. Stress-brain interaction in PTSD and BPD and the role of CT

As stated above, chronic or repeated stress has damaging effects on the brain, especially during development (Lupien et al., 2009). But what are the consequences of acute glucocorticoid exposure on neural activity in patient with PTSD or BPD and in participants with CT?

In the following section, I focus on results concerning effects of glucocorticoids on memory processes and its related brain regions, in both disorders and in participants with CT. Before delving into results concerning both disorders and participants with CT, I give a brief overview of the influence of stress hormones on neural activity and memory processes in healthy participants without CT.

The hippocampus (Sala et al., 2004), the amygdala (Mitra, Jadhav, McEwen, Vyas, & Chattarji, 2005), the PFC (Oei et al., 2007) and their connectivity (Henckens, van Wingen, Joels, & Fernandez, 2012; Hermans et al., 2014; Kruse, León, Stalder, Stark, & Klucken, 2018) are influenced by stress neuromodulators, such as cortisol, and these brain areas are rich in

corticosteroid receptors. Hydrocortisone leads to decreased negative RSFC of the amygdala to the middle frontal and temporal gyrus, possibly leading to a decreased influence of the amygdala on other brain structures (Henckens et al., 2012). Additionally, hydrocortisone provokes a reduced activation of the hippocampus and amygdala (Lovallo, Robinson, Glahn, & Fox, 2010). We previously investigated neural activity during AM retrieval after hydrocortisone administration in healthy participants, and found reduced activation in the anterior medial PFC (amPFC) (Fleischer et al., 2019). With regard to the effect of stress on memory processes in healthy participants, results showed, (to summarize briefly) an improvement in encoding and a deterioration in memory retrieval (Shields, 2020). Glucocorticoids seem to drive these effects (De Quervain, Schwabe, & Roozendaal, 2017).

The following chapters summarize literature on the influence of glucocorticoids on neural activity and functional connectivity and memory retrieval, in both patient groups and participants with CT.

1.4.1. Stress-brain interaction in PTSD

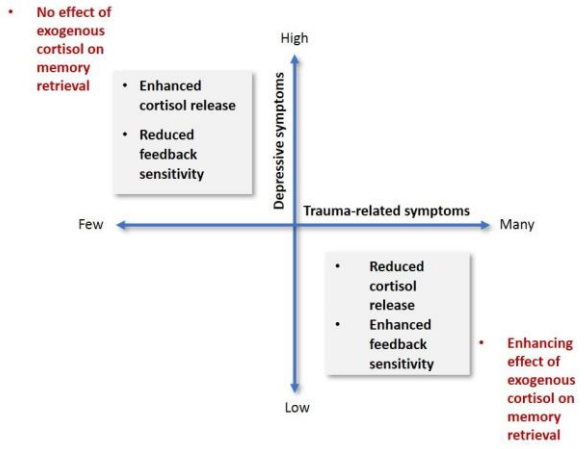
No study has yet investigated the influence of glucocorticoids on RSFC in patients with PTSD. Studies investigating the influence of glucocorticoids on neural activity and on memory retrieval in patients with PTSD are rare. A study using imaging techniques in patients with PTSD did not show any hydrocortisone-associated impairment in recall or retention in a declarative memory test. PET showed that patients with PTSD have a hydrocortisone-associated increase in hippocampal [^{18}F]FDG uptake under resting state conditions (Yehuda et al., 2010). Another study revealed similar opposing effects of hydrocortisone on glucose metabolic rate in amygdala, hippocampus and ACC (Yehuda et al., 2009). In line with these results, one of our previous studies showed that hydrocortisone improved memory retrieval in patients with PTSD, in contrast to healthy participants, who showed attenuated memory retrieval (Wingenfeld et al., 2012). Similar results in aging veterans have been described (Yehuda, Harvey, Buchsbaum, Tischler, & Schmeidler, 2007). Dexamethasone also impaired memory retrieval in healthy participants, while no such effect was seen in patients with PTSD (Bremner et al., 2004). However, another study showed a greater decline in verbal declarative memory retention after hydrocortisone treatment in patients with PTSD than in healthy participants. The authors, however, reported an inverse relationship between lymphocyte GR density and working memory performance in patients with PTSD (Grossman et al., 2006). These results suggest that GR expression may be particularly relevant to memory processes. Taken together, results suggest that hydrocortisone has opposing effects in patients with PTSD

and healthy participants: improved memory retrieval and activation of related brain regions in patients with PTSD, versus attenuated memory retrieval and activation in related brain regions in healthy participants. As yet, however, no study has investigated neural activity *during* memory retrieval in patients with PTSD. Neither has any study investigated the effect of hydrocortisone on RSFC in patients with PTSD. Therefore, a further aim of the current dissertation project is to investigate the effects of glucocorticoids on RSFC and on neural activity during memory retrieval in patients with PTSD.

1.4.2. Stress-brain interaction in BPD

Far less attention has been given to the effect of glucocorticoids in patients with BPD. No imaging study to date has investigate the effect of glucocorticoids in patients with BPD. As in patients with PTSD, it has been shown that patients with BPD showed improved memory retrieval after hydrocortisone administration, in contrast to to healthy participants, who showed decreased memory performance (Wingenfeld et al., 2013). Given that patients with PTSD and BPD showed similar results, the authors speculated that these effects might be related to traumatic experiences, more specifically to CT (see figure 6). Mineralocorticoid receptor (MR) stimulation with fludrocortisone resulted in no such effect in patients with BPD (Fleischer et al., 2015), again suggesting that the result might be related to GR expression. As imaging studies investigating the effect of glucocorticoids in patients with BPD are still lacking, a further aim of the current dissertation project is to investigate the effects of glucocorticoids on neural activity during memory retrieval and on RSFC in patients with BPD.

Figure 6. Psychopathology in two possible dimensions, HPA axis dysregulation and the effect of cortisol on memory retrieval.

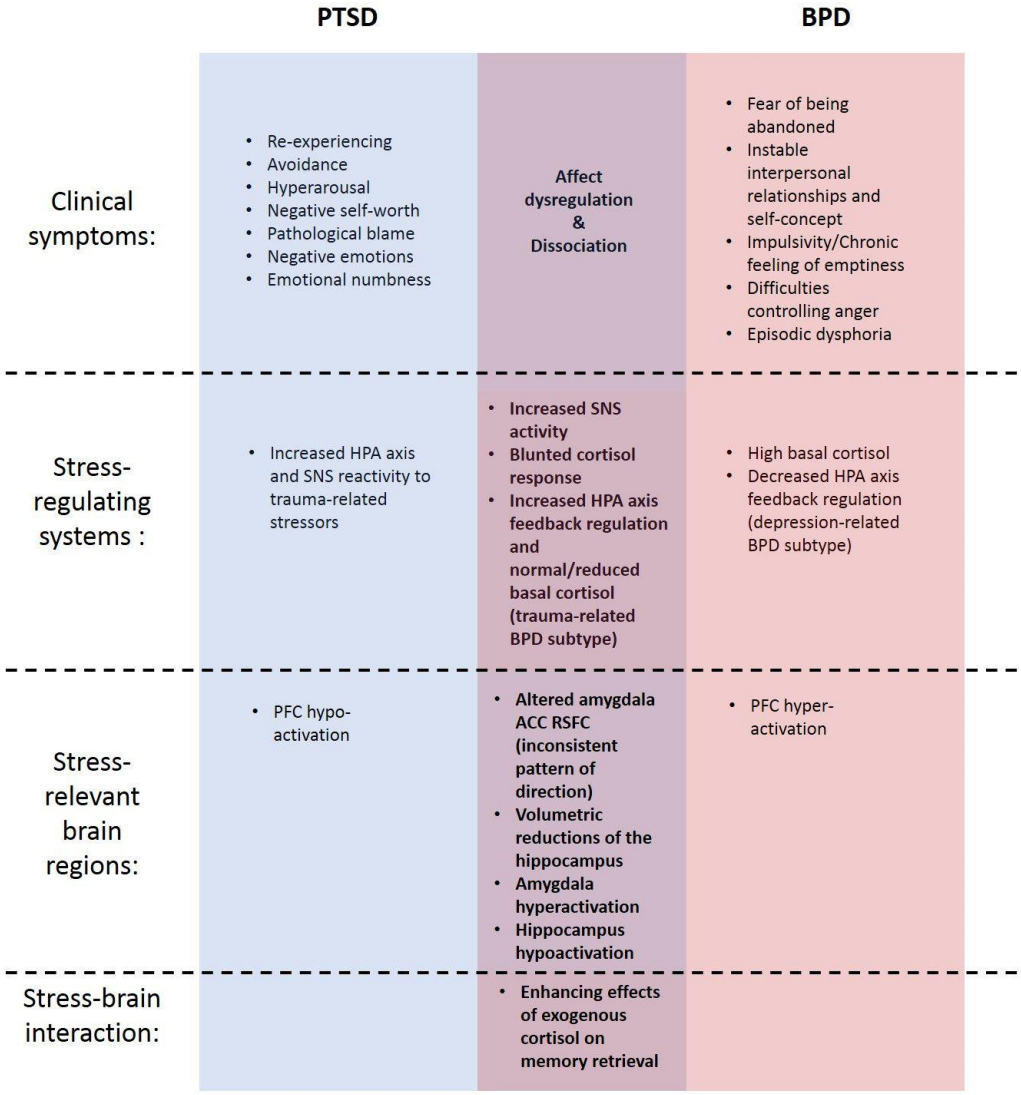


Psychopathology in two possible dimensions related to depressive symptoms and trauma-related symptoms resulting in differences in HPA axis regulation and effects of exogenous cortisol on memory retrieval according to (Katja Wingenfeld, Spitzer, Rullkötter, et al., 2010).

1.4.3. Overlapping features of PTSD and BPD in the stress-brain interaction

As stated above, previous studies suggest an increase, in terms of normalization, in memory retrieval in patients with PTSD and BPD following hydrocortisone administration (Wingenfeld et al., 2013; Wingenfeld et al., 2012) and provide evidence for an enhancing effect of hydrocortisone on neural activity, at least in patients with PTSD (Yehuda et al., 2010). As some authors have speculated that these effects might be related to CT (Wingenfeld et al., 2013; Wingenfeld et al., 2012), the next chapter reviews the role of CT in the enhancing effects of hydrocortisone.

Figure 7. Clinical symptoms, stress-regulating systems, stress-relevant brain regions and the stress-brain interaction in PTSD and BPD.



Schematic representation of overlapping symptoms and characteristics of HPA axis, SNS and HPA axis feedback regulation, neuroimaging findings and effects of glucocorticoids in PTSD and BPD. SNS = Sympathetic nervous system, HPA axis = Hypothalamic-pituitary-adrenal axis, GR = Glucocorticoid receptor, PTSD = Posttraumatic Stress Disorder, BPD = Borderline Personality Disorder, PFC = Prefrontal cortex, ACC = Anterior cingulate cortex, RSFC = Resting state functional connectivity.

1.4.4. The role of CT in overlapping features of PTSD and BPD in the stress-brain interaction

Since patients with PTSD and patients with BPD both report a high rate of CT**,** the authors suggest that hydrocortisone administration might lead to a normalization of memory retrieval processes in these patient groups with CT (Wingenfeld et al., 2013; Wingenfeld et al., 2012). Previous findings in rats supports this view. Long-term potentiation (LTP) is impaired and number of hippocampal MRs and GRs is reduced in adult rodents with low maternal care experiences. Glucocorticoid treatment enhanced LTP in these animals, but impaired LTP in control animals with high maternal care experiences (Champagne et al., 2008). Therefore, hydrocortisone may normalize HPA axis functioning and LTP caused by changes in MR and GR functioning in participants with CT, but has impairing effects in healthy participants without CT.

Taken together, findings suggest that low maternal care or CT may affect MR and GR density in the hippocampus. This might lead to opposing effects of glucocorticoids on memory retrieval and on neural activity in patients with PTSD and BPD. Figure 7 gives an overview of overlapping symptoms, characteristics of stress-regulating systems and stress-relevant brain regions and effects of glucocorticoids in PTSD and BPD.

The following chapter summarizes these findings in patients with PTSD and BPD and their association with CT. In addition, I outline which research questions still need to be addressed to better describe overlapping alterations in stress-regulating systems, stress-relevant brain regions and their interplay in patients with PTSD and BPD, and to understand the role of CT as mutual environmental and possible causal factor.

1.5. Summary and open questions

PTSD and BPD share symptoms such as affect dysregulation and dissociation and show a high prevalence of CT. In addition, high basal SNS activity and a blunted cortisol stress response to psychosocial stress characterize both patient groups and participants with CT. Furthermore, a BPD trauma-related subtype shows additional overlapping features such as low basal cortisol and enhanced feedback regulation of the HPA axis. However, HPA axis and SNS reactivity in response to a psychosocial stressor are less well investigated in patients with PTSD. So far, many studies used trauma-related stimuli.

Concerning neuroimaging studies, results hint towards an overactive amygdala with disrupted ACC functional connectivity and a hypoactive hippocampus in all three groups. This might partly be related to fear generalization and threat anticipation. However, studies

investigating hippocampus RSFC have yielded heterogeneous results, and no study to date has examined hippocampus and amygdala RSFC in the same design in patients with PTSD and BPD. Nor has any study investigated the influence of glucocorticoids on RSFC in patients with PTSD and BPD.

Hydrocortisone has opposing effects on memory retrieval in healthy participants as compared to patients with PTSD and BPD: improved retrieval in patients with PSTD and BPD, but attenuated memory performance in healthy participants. No imaging study has yet investigated the effect of glucocorticoids on neural activity during memory retrieval in patients with BPD and PTSD.

In the following, I outline how the current dissertation project aims at investigating these open questions.

2. Aims and design of the dissertation project

The main aim of this dissertation project is to further illuminate common and distinct features of PTSD and BPD, and to investigate the role of CT as one factor explaining variance in strongly overlapping features. To do so, study one of the current dissertation project focusses on stress-regulating systems, study two and three on stress-relevant brain regions and their interaction with stress-regulating systems. In brief, the three studies of the current dissertation project investigated:

1) HPA axis and SNS reactivity to psychosocial stress in patients with PTSD (Metz et al., 2020).

Metz, S., Duesenberg, M., Hellmann-Regen, J., Wolf, O. T., Roepke, S., Otte, C., & Wingenfeld, K. (2020). Blunted salivary cortisol response to psychosocial stress in women with posttraumatic stress disorder. *Journal of Psychiatric Research*.

2) Amygdala and hippocampus RSFC and the influence of hydrocortisone administration on amygdala and hippocampus RSFC in patients with PTSD and BPD (Metz, et al., 2019).

Metz, S., Fleischer, J., Grimm, S., Gärnter, M., Golde, S., Duesenberg, M., Roepke, S., Wolf, OT., Otte, C. & Wingenfeld, K. (2019). Resting-state functional connectivity after hydrocortisone administration in patients with post-traumatic stress disorder and borderline personality disorder. *European Neuropsychopharmacology*, *29*(8), 936-946.

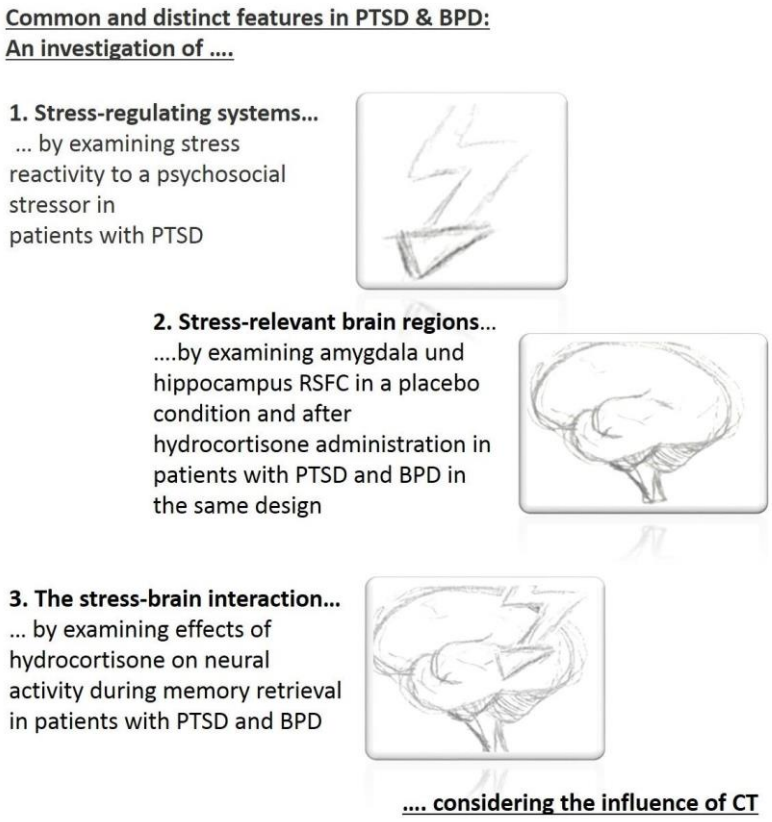
3) The influence of hydrocortisone on neural activity during AM retrieval in patients with PTSD and BPD (Metz, et al., 2019).

Metz, S., Fleischer, J., Gärnter, M., Golde, S., Duesenberg, M., Roepke, S., Wolf, OT., Otte, C. & Wingenfeld, K. (2019). Effects of hydrocortisone on autobiographical memory retrieval in patients with posttraumatic stress disorder and borderline personality disorder: the role of childhood trauma. ***Neuropsychopharmacology*****, *44*(12), 2038-2044.**

In all three studies, CT was investigated as a potential causal factor explaining variance.

Figure 8 summarizes very concisely the aims of the current dissertation project, and the following chapter outlines the rationale, research questions and hypotheses in more detail.

Figure 8. Aims of the current dissertation project in a nutshell.



PTSD = Posttraumatic stress disorder, RSFC = resting state functional connectivity, BPD = Borderline personality disorder, CT = childhood trauma.

2.1. Research questions and hypothesis

Research questions and corresponding hypothesis of each study are formulated in detail below. The rational and study design to address these specific hypotheses are also outlined.

2.1.1. Study 1: Psychophysiological stress response in PTSD

As stated above (chapter 1.2.1.), studies investigating the response to psychosocial stress in patients with PTSD are rare, as most studies have used trauma-related stimuli. There is initial evidence for attenuated reactivity of the HPA axis to psychosocial stress in patients with PTSD. Psychosocial stress-induced changes of the SNS are even less well investigated and results are heterogeneous. In response to trauma-related stressors, patients with PTSD revealed increased SNS activity. Therefore, the aim of study one is to (1) investigate the physiological and subjectively perceived stress response to a psychosocial stressor in female patients with PTSD. In addition, (2) the role of CT in HPA axis and SNS functioning in female patients with PTSD will be examined. The following hypotheses were formulated:

Hypotheses

(1) Female patients with PTSD show a blunted cortisol response but enhanced SNS activity in response to a psychosocial stressor compared with healthy women. (2) The cortisol response correlates negatively and SNS reactivity correlates positively with severity of CT in patients with PTSD.

2.1.2. Study 2: Hippocampus and amygdala RSFC in PTSD and BPD

There is growing evidence for disrupted amygdala ACC RSFC (chapter 1.3.1.) in both PTSD and BPD, and in participants with CT. Results concerning hippocampus RSFC have been heterogeneous. Hippocampus and amygdala RSFC have not been investigated in the same design in patients with PTSD and BPD. In addition, no study to date has examined the influence of hydrocortisone on amygdala and hippocampus RSFC in both patient groups. Therefore, the aim of study two was: (1) to investigate differences in hippocampus and amygdala RSFC in female patients with PTSD and in female patients with BPD and (2) to examine in an explanatory manner the effects of hydrocortisone administration on hippocampus and amygdala RSFC in female patients with PTSD, in female patients with BPD, and in healthy women. In addition, (3) the role of CT in RSFC and in the influence of hydrocortisone on RSFC will be examined. The following hypotheses were formulated:

Hypotheses

(1) Hippocampus and amygdala RSFC differ in female patients with PTSD and female patients with BPD, compared with healthy women. (2) Differences in amygdala and hippocampus RSFC correlate with severity of CT. (3) Effects of hydrocortisone administration on amygdala and

hippocampus RSFC differ between healthy women and female patients with PTSD and BPD, and correlate with severity of CT.

2.1.3. Study 3: Effects of hydrocortisone on autobiographical memory retrieval in PTSD and BPD

Patients with PTSD and BPD showed improved memory retrieval performance after hydrocortisone administration, in contrast to healthy participants, who showed decreased memory retrieval performance (chapter 1.4.1. and 1.4.2.). Similar results have been reported for participants with CT. Therefore, the aim of study three was to investigate neural activity during AM retrieval after hydrocortisone administration in female patients with PTSD and in female patients with BPD, as compared with healthy women. Furthermore, the role of CT in these processes will be examined. The following hypotheses were formulated:

Hypotheses

Hydrocortisone administration leads to the following: (1) reduced activation of the AM related brain regions, hippocampus, PFC, ACC, posterior cingulate cortex (PCC), and the superior and middle temporal gyri in healthy women. (2) An increased activation of these brain regions in female patients with PTSD and in female patients with BPD and (3) CT correlates positively with increased activation of these brain regions following hydrocortisone administration.

2.2. Rationale of the three studies

In this chapter the rationale of the three studies will be outlined. Study designs and procedures will be described, to explain how they extend existing literature (chapter 1) and how they aim to answer the hypotheses of the current dissertation project (chapter 2.1.).

All studies were conducted at the Charité - Universitätsmedizin Berlin, Klinik für Psychiatrie und Psychotherapie, Campus Benjamin Franklin, Germany. The studies were carried out in accordance with the latest version of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to participation. The studies were approved by the local ethics committee. All studies were supported by Deutsche Forschungsgemeinschaft (DFG) [DFG-Grant WI 3396/2–3 to KW, OTW and CO].

2.2.1. Participants

We recruited inpatients and outpatients at the Charité Universitätsmedizin Berlin, Klinik für Psychiatrie und Psychotherapie, Campus Benjamin Franklin, Germany. Outpatients and healthy

women were recruited via online advertisement and received financial remuneration (100 euros). We assessed psychiatric diagnosis by Structured Clinical Interview for DSM-IV axis I and II (SCID) (Wittchen, Zaudig, & Fydrich, 1997). Exclusion criteria were central nervous system, autoimmune or somatic diseases, metabolic or endocrine disorders, infections at the time of study participation, pregnancy, and a body mass index (BMI) below 17.5 and above 30 kg/m^2. Further exclusion criteria for healthy women were any DSM-IV axis I or axis II disorder, a history of psychiatric or psychotherapeutic treatment as well as intake of any medication. Further exclusion criteria for female patients with PTSD (all studies) and patients with BPD (study two and three) were current episode of major depressive disorder, schizophrenia, schizoaffective disorder, bipolar disorder, anorexia, alcohol or drug dependency. Any participants with fMRI contraindications (e.g., non-removable metals) were also excluded in study two and three.

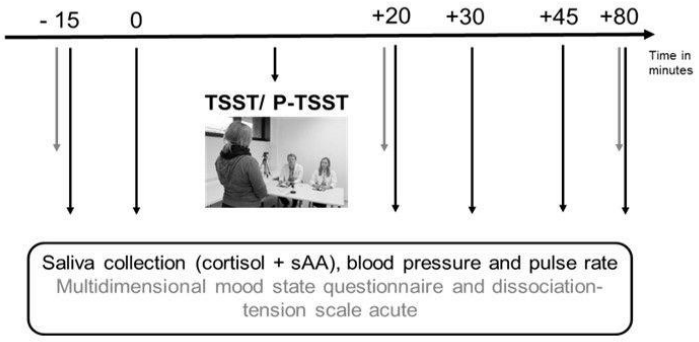
In all three studies we used the childhood trauma questionnaire (CTQ) to assess traumatic childhood experiences (Bernstein, Ahluvalia, Pogge, & Handelsman, 1997; Wingenfeld et al., 2010). PTSD symptoms according to the DSM-IV were assessed using Post-traumatic Stress Diagnostic Scale (PDS-r) (Foa, 1995). We used the Borderline Symptom List (BSL-23) to measure severity of borderline symptoms (Bohus et al., 2009). Figure 9 illustrates the study design of study one and figure 10 illustrates the study design of study two and three (for additional study specific questionnaires see chapter 3-5).

2.2.2 Procedure

All three studies were placebo-controlled crossover designs. In the first study (psychosocial stress reactivity in patients with PTSD) participants were randomized to TSST or control condition. The second and third study (imaging studies), involving hydrocortisone and placebo administration, were part of the same project and double-blinded. In all three studies, participants underwent the treatment and placebo condition with at least a one-week interval between them.

The TSST incorporates a preparation phase, a job interview, and an arithmetic task in front a committee and participants are told that they would be recorded by a video camera (overall duration 20 minutes) (Kirschbaum et al., 1993). The placebo TSST (P-TSST) does not include stressful components but is otherwise similar to the TSST (Het, Rohleder, Schoofs, Kirschbaum, & Wolf, 2009) (see figure 9 for details on study procedure).

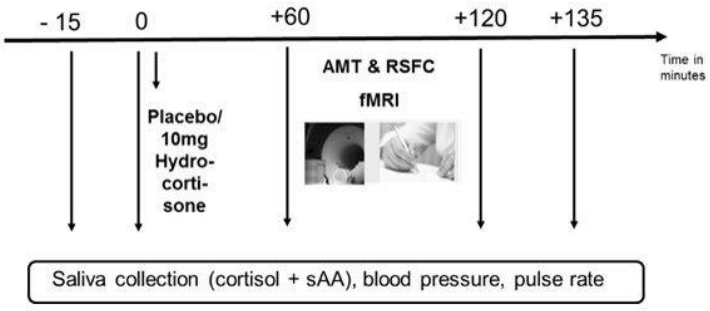
Figure 9. Study design of study one.



Saliva collection: 15 minutes before, immediately before (0 minutes), and 20, 30, 45 and 80 minutes after TSST and P-TSST. Abbreviations: TSST = Trier social stress test, P-TSST = Placebo trier social stress test, sAA = salivary alpha amylase activity.

In the imaging studies, 10 mg hydrocortisone GALEN® was administered to investigate the influence of glucocorticoids on RSFC and on neural activity during AM retrieval. Hydrocortisone is a synthetic glucocorticoid, which binds to GR and MR. Time of administration was based on the pharmacodynamics of the drug: according to the summary of product characteristics, hydrocortisone peaks within one hour and has an elimination half-life of 1 ½ hours. An identical looking placebo was administered at the same respective times (see figure 10 for details on study procedure).

Figure 10. Study design of study two and three.



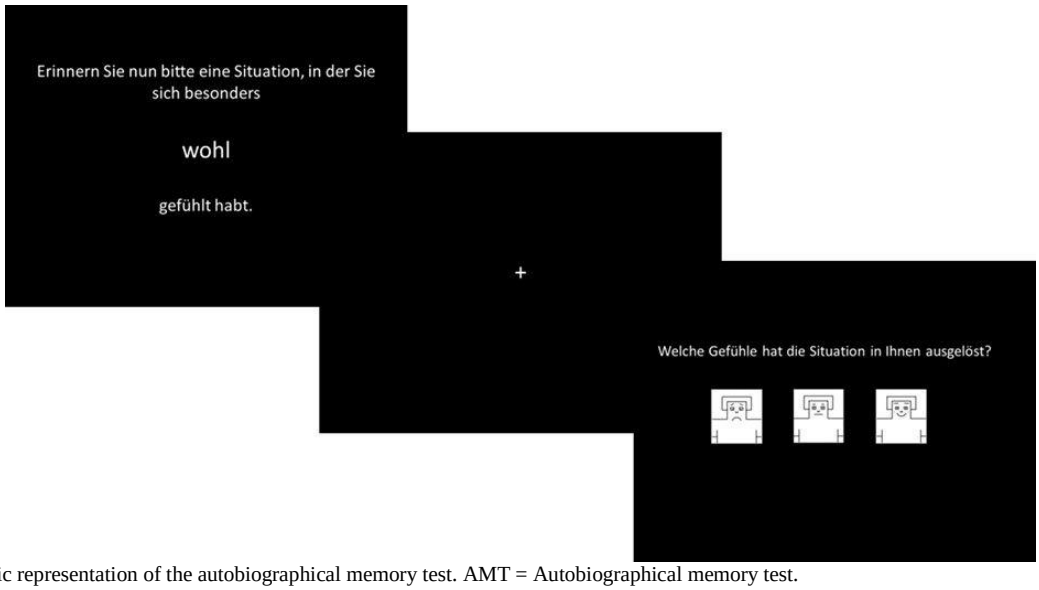
Saliva collection: 15 minutes before, immediately before (0 minutes), and 60, 120 and 135 minutes after placebo or hydrocortisone administration. Abbreviations: AMT = Autobiographical memory test, RSFC = Resting state functional connectivity, fMRI = functional magnet resonance imaging, sAA = salivary alpha amylase activity.

2.2.3. Autobiographical memory test (AMT)

The AMT for fMRI scanning was first used and designed by Young et al. (Young et al., 2012). The AMT is a memory test in which cue words are presented and participants are instructed to recall a specific memory in response to the cue word. We adapted the version of Young et al. for the current study. We used two versions of the AMT, both of which contained 25 adjectives

as cue words. Both versions were counterbalanced across conditions and stimuli were presented in randomized order. Similarly to Young et al. (Young et al., 2012), positive, neutral or negative cue words were presented and participants were instructed to recall a specific event from their past in response to the cue words. Cue words were presented for 15 s. In response to the cue word, participants had to indicate whether they found a fitting memory via button press on the response box. A fixation cross was then presented for 10 s during which the participants were instructed to recall the AM. Female patients and healthy women then rated valence, arousal, and recency of the retrieved memory by pressing the corresponding button on the response box (see figure 11). A simple arithmetic problem was used as a distractor task. Participants underwent three practice trials outside the scanner.

Figure 11. AMT.



Schematic representation of the autobiographical memory test. AMT = Autobiographical memory test.

2.2.4. Measurement of saliva sampling, blood pressure and heart rate

We used Salivette® collection devices (Sarstedt, Germany) to sample saliva. Samples were stored at -80 °C. Biochemical analysis were performed in the Neurobiology Laboratory of the Dept. of Psychiatry, Charité – Universitätsmedizin Berlin, Germany. We analyzed cortisol using an adapted homogenous time-resolved fluorescence resonance energy transfer (HTR-FRET)-based competitive immunoassay (Duesenberg et al., 2016). Salivary alpha amylase (sAA) activity was analyzed with modifications as previously described (Rombold et al., 2016).

Blood pressure and pulse rate were assessed in all three studies. The automatic device *boso medicus uno* from Bosch Sohn Germany was used for this purpose in all three studies.

Participants were seated in a standardized position and were instructed to refrain from movement during measurement.

2.2.5. Measurement of brain imaging

The software Presentation (Neurobehavioral Systems, Inc.) and the audio-visual stimulation technology VisuaStim Digital (Resonance Technology Company, Inc.) were used to present stimuli. A Siemens Magnetom TrioTim (3T) scanner with a 12-channel receiver coil array and an echoplanar imaging (EPI) pulse sequence (3.0 mm slices acquired sagittally, repetition time = 2000 ms, echo time = 30 ms, flip angle = 70°, matrix = 64 × 64, field of view = 192 mm, voxel size = 3 × 3 × 3 mm) was used to obtain scans. 180 EPI images were acquired during resting state scans. Number of EPI images during the AMT varied depending on the number of recalled memories with a maximum of 900 EPI images. For co-registration, high-resolution T1-weighted anatomical MRI scans were acquired.

Having introduced the aims, design and rationale of the three studies, I will now present the original publication of these studies (chapter 3, 4, and 5). Supplementary material of study one and three of the original publications can be found in the appendix.

3. Study 1: Psychophysiological stress response in PTSD

Blunted salivary cortisol response to psychosocial stress in women with posttraumatic stress disorder

This chapter was published as:

Metz, S., Duesenberg, M., Hellmann-Regen, J., Wolf, O. T., Roepke, S., Otte, C., & Wingenfeld, K. (2020). Blunted salivary cortisol response to psychosocial stress in women with posttraumatic stress disorder. *Journal of Psychiatric Research, 130*, 112-119.

DOI: 10.1016/j.jpsychires.2020.07.014

https://doi.org/10.1016/j.jpsychires.2020.07.014

4. Study 2: Hippocampus and amygdala RSFC in PTSD and BPD

Resting-state functional connectivity after hydrocortisone administration in patients with post-traumatic stress disorder and borderline personality disorder

This chapter was published as:

Metz, S., Fleischer, J., Grimm, S., Gärnter, M., Golde, S., Duesenberg, M., ... & Wingenfeld, K. (2019). Resting-state functional connectivity after hydrocortisone administration in patients with post-traumatic stress disorder and borderline personality disorder. *European Neuropsychopharmacology*, *29*(8), 936-946.

DOI: 10.10116/j.euroneuro.2019.05.008

https://doi.org/10.1016/j.euroneuro.2019.05.008

5. Study 3: Effects of hydrocortisone on autobiographical memory retrieval in PTSD and BPD

Effects of hydrocortisone on autobiographical memory retrieval in patients with posttraumatic stress disorder and borderline personality disorder: the role of childhood trauma

This chapter was published as:

Metz, S., Fleischer, J., Gärnter, M., Golde, S., Duesenberg, M., Roepke, S., ... & Wingenfeld, K. (2019). Effects of hydrocortisone on autobiographical memory retrieval in patients with posttraumatic stress disorder and borderline personality disorder: the role of childhood trauma. *Neuropsychopharmacology*, *44*(12), 2038-2044.

DOI: 10.1038/s41386-019-0459-8

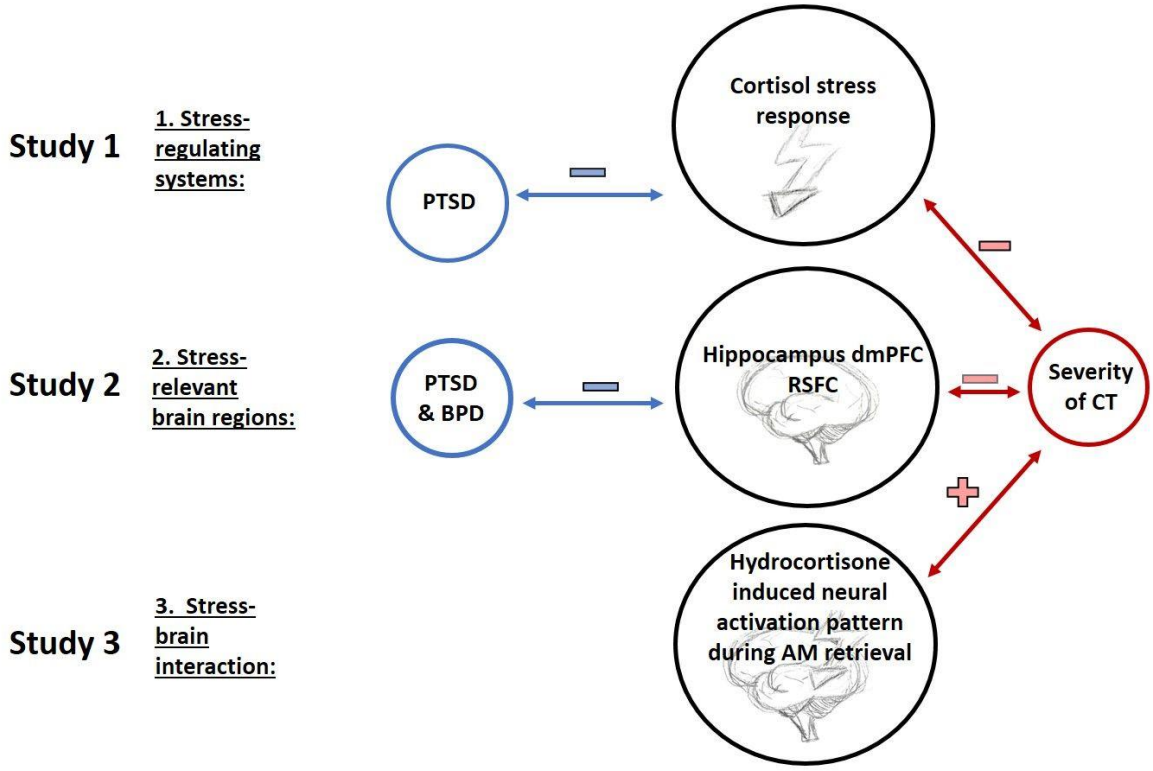
https://doi.org/10.1038/s41386-019-0459-8

6. General Discussion

The main aim of this dissertation project was to further illuminate overlapping features of PTSD and BPD in stress-regulating systems, stress-relevant brain regions and their interplay to better explain the evolution of clinical symptoms, such as affect dysregulation and dissociation, that characterize both disorders. As a secondary aim, the role of CT as one factor explaining variance in especially overlapping features was examined. We, therefore, conducted the three above described studies. Results of this dissertation project are as follows: First, female patients with PTSD were characterized by a blunted cortisol response to a psychosocial stressor, compared to healthy women. Measure of cortisol changes over time in response to a psychosocial stressor correlated negatively with severity of CT. SNS reactivity was not increased in female patients with PTSD; we found evidence for a less pronounced sAA response to the TSST. No association with CT was found. In only partial agreement with previous findings suggesting higher basal SNS activity in patients with PTSD, we found a trend for higher basal diastolic blood pressure in patients with PTSD, but no differences in sAA activity or systolic blood pressure. Secondly, hippocampus dmPFC RSFC is reduced in female patients with PTSD and BPD. Hippocampus dmPFC RSFC correlated negatively with severity of CT and clinical symptoms. There were no differences between female patients with PTSD and BPD and healthy women in amygdala RSFC. In addition, there was no influence of hydrocortisone on either amygdala or hippocampus RSFC, nor was there an interaction of hydrocortisone with group. Thirdly, female patients with PTSD and BPD and healthy women did not differ in their neural activity during AM retrieval, neither in the placebo condition nor after hydrocortisone administration. Severity of CT correlated with a hydrocortisone induced pattern of neural activity.

Figure 12 depicts a summary of results.

Figure 12. Summary of results (study 1, 2 and 3).



Schematic representation of findings in PTSD and BPD of the current dissertation project. CT = Childhood trauma, PTSD = Posttraumatic stress disorder, BPD = Borderline personality disorder, dmPFC = Dorsomedial prefrontal cortex, RSFC = Resting state functional connectivity, AM = Autobiographical memory.

In the following chapters (chapter 6.2.1, 6.2.2., 6.2.3. and 6.2.4.), the findings related to HPA axis, SNS, amygdala and hippocampus RSFC, and to hydrocortisone induced AM-related neural activity pattern in patients with PTSD and BPD, will be discussed in the light of the existing body of literature. In each of these chapters, I only shortly address the role of CT as one factor explaining differences between patient groups and healthy participants. Chapter 6.3. then focusses explicitly on the role of CT to integrate results into a theoretical model revealing mechanisms that link CT and the psychopathology of PTSD and BPD. Chapter 6.4. delineates these results' implications for future research. Finally, the conclusion of this dissertation project (chapter 6.5.) summarizes the main findings. Prior to discussing the findings of the current dissertation project, the following chapter summarizes strengths and limitations of the three studies, which should be kept in mind while reading the discussion.

6.1. Strengths and limitations of the studies

The following strengths and limitations should be borne in mind while interpreting the results.

Strengths: In all three studies, the majority of patients were unmedicated and had very few comorbid mental disorders. Major depressive disorder as a comorbidity was an exclusion

criteria because it affects HPA axis regulation (Wingenfeld et al., 2013). Furthermore, all three studies used within-subject designs including a non-stressful control condition or a placebo condition for comparison. This reduces error variance resulting from natural variance between individuals. In addition, all three studies had comparatively large sample sizes, with an overall sample size of 50 participants in study one and over 70 participants in both studies two and three. This is especially worth mentioning as previously only one study had investigated the influence of glucocorticoids on memory retrieval and neural activity in patients with PTSD, and that included only 12 patients with PTSD (Yehuda et al., 2010). All three studies only included female patients with PTSD and BPD and healthy women, and groups did not differ in menstrual cycle phase. Former studies reported sex differences in the stress response in both healthy participants and patients (Kudielka, Buske-Kirschbaum, Hellhammer, & Kirschbaum, 2004; Paris et al., 2010), in amygdala RSFC (Wu et al., 2016) and in the association of cortisol and amygdala RSFC (Kogler et al., 2016). Furthermore, an impact of menstrual cycle on cortisol output has been suggested (Wolfram, Bellingrath, & Kudielka, 2011). We therefore reduced variance related to menstrual cycle and gender. In addition, the group of patients with PTSD and BPD included a high number of women who had experienced sexual abuse before the age of 18. The homogeneity of the sample considering type of trauma can be interpreted as a further strength of the study

Limitations: First, there are several limitations that concern all studies. Since we only included women, results of all three studies are not generalizable to men. Furthermore, we did not include a control group with trauma-exposed healthy participants. It is, therefore, not possible to precisely disentangle the effects of CT and psychopathology on stress reactivity, RSFC, and the effects of glucocorticoids on neural activity. The interpretation concerning the role of CT remains somewhat speculative. An association of former disorders with GR promotor methylation and therefore with stress reactivity (see chapter 6.3. for details on GR promotor methylation and stress reactivity) has been shown (Tyrka et al., 2016). Comorbidities such as lifetime substance abuse or previous MDD may have influenced the result. However, exclusion of all current or lifetime comorbid mental disorder would have led to an artificial sample because comorbid disorders are frequent in patients with PTSD and BPD. In addition, no information about previous treatment was collected. As psychotropic medication (Manthey et al., 2011; Wagner, de la Cruz, Köhler, & Bär, 2017) and psychotherapy (King et al., 2016; Mommersteeg, Keijsers, Heijnen, Verbraak, & van Doornen, 2006) both influence cortisol levels and RSFC, this might have been relevant to the current studies. Current psychotropic medication was, however, an exclusion criterion in study two and three. Trauma during

adulthood was also frequent in both groups and may have influenced the results. Previous findings suggested that the timing of CT might affect different domains due to distinct timing of development of brain regions (Lupien et al., 2009). Whereas early postnatal experience might influence sensory integration and self-regulation, later experience might influence cognitive processes (Hambrick, Brawner, & Perry, 2019). Furthermore, it has been suggested that different types of trauma (e.g. abuse vs. neglect) influence different types of domains (e.g., executive functioning vs. affective processing/cognitive inhibition) (Gould et al., 2012; Henderson, Hargreaves, Gregory, & Williams, 2002).

Concerning study two and three, the dosage of 10 mg hydrocortisone was low compared with other fMRI studies (Symonds, McKie, Elliott, Deakin, & Anderson, 2012) which may account for the absence of group differences. However, small dosages may more closely mimic the actual physiological stress response. In addition, hydrocortisone stimulates the MR and the GR. Therefore, it is impossible to conclude whether differences in neural activity are related to MR or GR stimulation. Previous studies have shown an enhancing effect of hydrocortisone on memory retrieval (Wingenfeld et al., 2013) but no effect of fludrocortisone (MR stimulation) on AM retrieval (Fleischer et al., 2015) and even an impairing effect of fludrocortisone on hippocampus mediated memory processes (Wingenfeld et al., 2015) in patients with BPD. The differentiation of receptor specific effects in different brain regions is therefore worthy of investigation.

A specific limitation of study three is the missing behavioral data on AM performance. Collection of behavioral data is challenging in the MRI as it usually requires verbal or written statements by participants; verbal assessment during scanning leads to movement artefacts and memory recall after scanning may be inaccurate. This makes it difficult to compare the current findings with previous results (Wingenfeld et al., 2013; Wingenfeld et al., 2012).

As our patient samples predominantly include women exposed to sexual abuse before the age of 18, future studies should investigate whether similar results can be found in the context of different timing and type of trauma.

6.2. Discussion of the main findings

6.2.1. Psychosocial stress response in PTSD

Since stress reactivity to a psychosocial stressor in patients with PTSD has gained little attention so far, study one investigated the subjectively perceived and physiological stress response to a psychosocial stressor, the TSST, in patients with PTSD. As a secondary aim we examined the role of CT as one factor explaining alterations in stress-regulating systems. We hypothesized

that (1) female patients with PTSD show a blunted cortisol response but enhanced SNS activity in response to a psychosocial stressor, compared with healthy women. We additionally hypothesized that (2) the cortisol response correlates negatively and the SNS reactivity correlates positively with severity of CT in patients with PTSD. In accordance with our hypothesis, cortisol increase was blunted following the TSST, and measures of cortisol changes over time in response to a psychosocial stressor correlated negatively with severity of CT. Contrary to our hypothesis, we found no evidence for enhanced SNS reactivity after the TSST in female patients with PTSD. We even found evidence for a less pronounced sAA response to the TSST and no association with CT. Furthermore, female patients with PTSD had higher basal diastolic blood pressure on trend level. Concerning the subjectively perceived stress response, the TSST produced a more profound and long-lasting effect on subjective stress ratings resulting in worse mood, less wakefulness, and more dissociative symptoms in female patients with PTSD. Patients additionally reported worse mood and more dissociative symptoms at baseline.

We found blunted cortisol increase following a psychosocial stressor in female patients with PTSD, compared with healthy women. This is in line with previous findings showing a blunted cortisol response following psychosocial stress or the cold pressor test in patients with PTSD (Santa Ana et al., 2006; Wichmann et al., 2017; Zaba et al., 2015). Similar findings have been described in patients with BPD (Duesenberg et al., 2019; Scott, Levy, & Granger, 2013). A similar stimulated cortisol response has been demonstrated in veterans (Pierce & Pritchard, 2016) and females with a history of CT showed a similar stimulated cortisol response (MacMillan et al., 2009; Pierrehumbert et al., 2009). However, a higher cortisol response to psychosocial stress in individuals with CT has also been reported (Heim et al., 2000). This effect was, however, most robust in women with current symptoms of depression and anxiety. The authors suggested that increased CRH activity, as a marker for central HPA axis activation, might be associated with CT and might precede an altered cortisol response. Therefore, adaptation processes to enhanced CRH on lower levels of the HPA axis might result in low cortisol release in patients with PTSD and BPD (see figure 14) (Bhagwagar, Hafizi, & Cowen, 2005; Duesenberg et al., 2019; Oquendo et al., 2003; Scott et al., 2013; Wessa, Rohleder, Kirschbaum, & Flor, 2006), and high cortisol in depressive patients (Heim et al., 2000). More details on the proposed mechanism initiating increased CRH and enabling low cortisol can be found in chapter 6.3., which focusses on the role of CT.

We expected to find increased SNS activity in response to a psychosocial stressor in female patients with PTSD compared with healthy women. We found, however, a less pronounced

increase in sAA activity in female patients with PTSD in response to the TSST. No differences in blood pressure were found concerning stress reactivity. Previous studies also found no differences in blood pressure and heart rate (MacMillan et al., 2009; Zaba et al., 2015). However, as suggested by our hypothesis, others have found an increased heart rate response to a psychosocial stressor in patients with PTSD (Zaba et al., 2015) and increased sAA response in healthy participants with CT (Kuras et al., 2017), reflecting heightened SNS reactivity. What might be the reason for missing effects on blood pressure and sAA activity in our female patients with PTSD? As most studies have shown an association of PTSD with increased SNS reactivity in response to trauma-related stimuli (Geracioti et al., 2008; Liberzon et al., 1999; Orr et al., 2003), one might argue that a psychosocial stressor predominantly reveals differences in HPA axis reactivity in patients with PTSD, while more emotionally arousing stressors (e.g. trauma-related stimuli), reveal differences in SNS reactivity. Furthermore, as a correlation with CT has been demonstrated in former studies but not in our study, it awaits to be determined which of these effects are associated with PTSD and which with CT. Therefore, results concerning stimulated SNS in response to a psychosocial stressor remain heterogeneous in patients with PTSD.

Concerning findings on basal SNS activity, we found a trend for increased diastolic blood pressure in patients compared to healthy women, irrespective of stress induction. However, no difference between patients and healthy participants were found in basal systolic blood pressure and sAA activity. Previous studies have described increased basal SNS activity in patients with PTSD, including increased catecholamines (Pan et al., 2018), higher heart rate (Buckley et al., 2004; Paulus et al., 2013) and blood pressure (Muraoka et al., 1998). Increased SNS activity has also been shown in other adult anxiety disorders, BPD and individuals with CT. (Barber et al., 2019; Eddie et al., 2018; Heim et al., 2000; Otte et al., 2005; Wingenfeld et al., 2015). Results of study one are therefore only partly in line with the higher basal SNS activity in patients with PTSD and BPD and participants with CT proposed in chapter 1.2.3. Investigation of basal SNS activity was, however, not a primary aim of study one, which focused on HPA axis and SNS reactivity to a psychosocial stressor. The number of baseline measures are consequently limited and non-fasting.

Low stimulated cortisol might have, however, negative consequences on affect regulation. A mood-buffering effect of cortisol has been demonstrated (Het et al., 2012; Het & Wolf, 2007). Therefore, a blunted cortisol response in women with PTSD possibly attenuates a mood-buffering effect of cortisol. Accordingly, women with PTSD perceived themselves to be in a

worse mood, less wakeful, and having more dissociative symptoms than healthy women did following exposure to stress.

Taken together, our main results reveal a blunted stimulated cortisol response and increased negative affect in response to a psychosocial stressor in patients with PTSD. Similar results have been described for patients with BPD and for participants with CT, irrespective of diagnosis (chapter 1.2.3.). As blunted cortisol reactivity might be an adaptation process to enhanced CRH on lower levels of the HPA axis, and enhanced CRH might be associated with CT, the question arises of how CT leads to increased CRH? I present possible answers to this question in a hypothetical model linking CT to the psychopathology of PTSD and BPD (see chapter 6.3. for integration of results).

As alterations in stress-regulating systems are likely accompanied by alteration in stress-relevant brain regions, we investigated in a second study hippocampus and amygdala RSFC, and the influence thereon of hydrocortisone, in patients with PTSD and BPD.

6.2.2. Hippocampus and amygdala RSFC in patients with PTSD and BPD

Previous studies have shown hippocampal and amygdala alterations in both patient groups. As hippocampus RSFC yielded particularly heterogeneous results in patients with PTSD and BPD and study designs varied hugely, we investigated RSFC of the hippocampus in addition to amygdala RSFC in patients with PTSD and BPD within the same design. Furthermore, a blunted cortisol response (as revealed in chapter 6.2.1.) hints towards altered HPA axis reactivity in patients with PTSD. As the hippocampus and the amygdala have a high density of corticosteroid receptors, these regions seem promising targets for the investigation of effects of glucocorticoid administration. We therefore further examined the effects of hydrocortisone administration on amygdala and hippocampus RSFC. We hypothesized that (1) hippocampus and amygdala RSFC differ between female patients with PTSD and female patients with BPD compared with healthy women. We additionally hypothesized that (2) differences in amygdala and hippocampus RSFC correlate with severity of CT and that (3) effects of hydrocortisone administration on amygdala and hippocampus RSFC differ between healthy women and female patients with PTSD and BPD, and correlate with severity of CT. Both patient groups showed reduced RSFC between hippocampus and dmPFC in the placebo condition, which correlated negatively with severity of CT and severity of clinical symptoms. We found no differences in amygdala RSFC between groups. Furthermore, we did not find an effect of hydrocortisone on amygdala or hippocampus RSFC, nor an interaction of group with hydrocortisone.

Hippocampus dmPFC RSFC was decreased in female patients with PTSD and BPD, and correlated negatively with severity of CT and severity of clinical symptoms of both disorders. This is in line with the existing body of literature. Previous studies have shown weaker hippocampus mPFC RSFC in patients with PTSD (Jin et al., 2014; Malivoire, Girard, Patel, & Monson, 2018). It has also been shown that CT predicted greater RSFC between hippocampus and dmPFC, while PTSD symptoms predicted lesser RSFC (Birn, Patriat, Phillips, Germain, & Herringa, 2014). Direction of effects, therefore, seem to be inconsistent in relation to CT and in patients with PTSD, with former studies and the current results revealing increased and decreased RSFC. Despite the fact that differences in processing imaging data might results in different patterns of directionality (Marusak et al., 2016), results hint towards an association of CT with hippocampus mPFC RSFC. An involvement of both brain regions, hippocampus and mPFC, in the regulation of threat and arousal has been shown (Abdallah et al., 2017; Kim & Hamann, 2007; Lissek et al., 2014; Modinos, Ormel, & Aleman, 2010). Therefore, CT might lead to an altered pattern of hippocampus (d)mPFC RSFC. This might then cause a dysfunctional response to threat, in which the hippocampus (d)mPFC interaction has been implicated (Lissek et al., 2014). This might partially explain symptoms such as hyperarousal in PTSD (Norrholm & Jovanovic, 2018) and emotional dysregulation in BPD (Kamphausen et al., 2013). A more detailed explanation on how CT might alter hippocampus dmPFC RSFC can be found in chapter 6.3..

No differences in amygdala RSFC between female patients and healthy women were revealed, which contradicts our hypothesis and previous research. Former research focused especially on amygdala PFC RSFC and suggested increased amygdala activation and its disrupted RSFC to prefrontal regions particularly in patients with PTSD (Baczkowski et al., 2017; Stevens et al., 2013). Furthermore, a recent meta-analysis, including studies examining RSFC irrespective of disease status, suggested that amygdala ACC rather than amygdala PFC RSFC is disrupted in relation to internalizing disorders and risk factors such as CT (Marusak et al., 2016). However, the pattern of reported amygdala ACC RSFC was heterogeneous, with some studies reporting increased RSFC while others reported decreased RSFC (Marusak et al., 2016). Overall, the existing body of literature provides preliminary evidence that the amygdala ACC pathway might be central to the etiology of different disorders related to CT. In study two of this dissertation project, the absence of an intervention to create amygdala activation and insufficient sample size are factors possibly explaining the absence of effects in amygdala RSFC. This is in line with results of study one, showing no increased SNS activity in patients with PTSD. Taken together, missing results on SNS and amygdala activity suggest that these

may be more easily detected in response to emotionally arousing material as trauma-related stimuli.

In addition, we did not find any effects of hydrocortisone administration on hippocampus or amygdala RSFC across groups. No study has yet investigated the effect of hydrocortisone on amygdala or hippocampus RSFC in patients with PTSD or BPD. Concerning healthy participants, the current results contradict previous findings describing amygdala decoupling after hydrocortisone administration (Henckens et al., 2012) and an influence of a psychosocial stressor resulting in increased connectivity between the hippocampus and amygdala, ACC, and OFC (Kruse et al., 2018). However, differences in total number of scans, timing, investigated parameters and method of stress induction render a direct comparison of effects difficult. As no study has yet compared the effects of hydrocortisone administration on RSFC in both disorders and healthy participants, explanations about missing results remain speculative. Opposing effects of hydrocortisone on memory retrieval have been shown in patients with PTSD and BPD compared with healthy participants, with an improving effect in patients and deteriorating effect in healthy participants (Wingenfeld et al., 2013; Wingenfeld et al., 2012). It is possible that this opposing effect only occurs during task-related neural activity and not during rest. Therefore, in a third study, we investigated the effect of hydrocortisone on neural activity during AM retrieval in patients with PTSD and BPD. Results are presented in the following chapter.

Taken together, patients with PTSD and BPD are characterized by decreased hippocampus dmPFC RSFC, which is related to CT and possibly explains a lack of reduction in the fear response present in both disorders (see figure 12 for summary of results).

6.2.3. Effects of hydrocortisone administration on neural activity during AM retrieval in patients with PTSD and BPD

As previous studies have suggested enhanced memory retrieval after glucocorticoid administration in patients with PTSD and BPD, in contrast to reduced memory retrieval in healthy participants (Wingenfeld et al., 2013; Wingenfeld et al., 2012), we investigated the effects of glucocorticoids on neural activity during memory retrieval. We hypothesized that hydrocortisone administration leads to the following: (1) reduced activation of the AM related brain regions, hippocampus, PFC, ACC, PCC, and the superior and middle temporal gyri in healthy women; (2) an increased activation of these brain regions in female patients with PTSD and in female patients with BPD and that (3) CT correlates positively with increased activation of these brain regions after hydrocortisone administration. We did not find any differences in neural activity during AM retrieval between healthy participants and patients with PTSD and

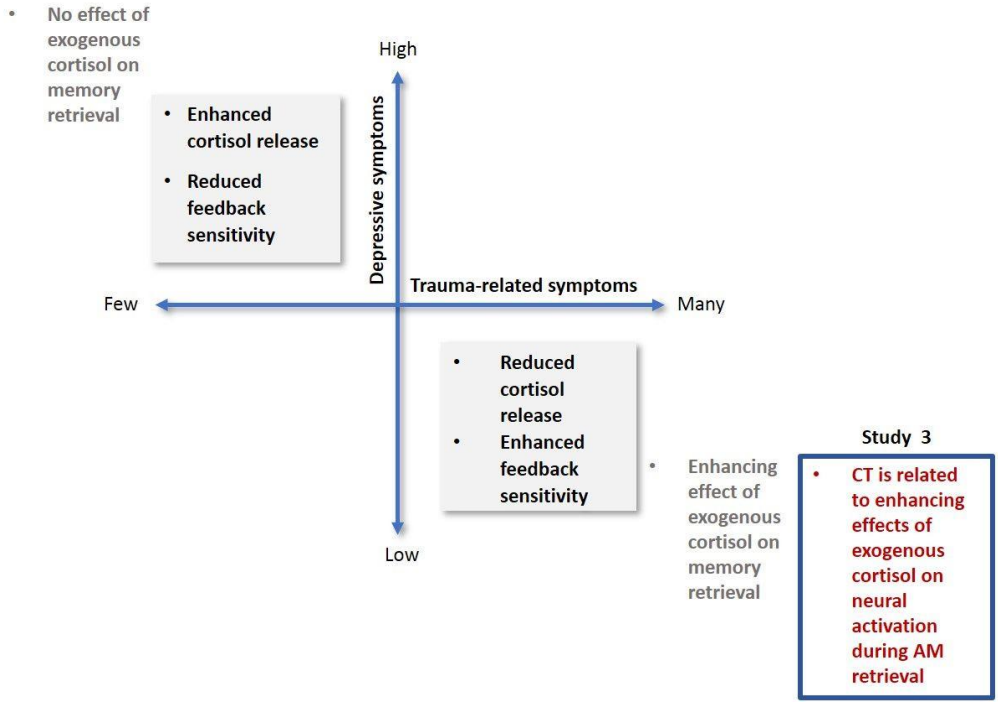
BPD, neither in the placebo condition nor after hydrocortisone administration. Severity of CT, however, correlated with hydrocortisone effects during AM retrieval in the amPFC, vlPFC, PCC, angular gyrus, and cerebellum: specifically, more CT was associated with higher activation in the hydrocortisone condition compared with the placebo condition in these brain areas.

Contradicting hypothesis one and two, we found that neural activity during AM retrieval did not differ between female patients and healthy women after administration of placebo or hydrocortisone. Thus, we did not see the expected decrease in brain activation (namely in the hippocampus) in response to hydrocortisone in the control group nor the respective expected increase in female patients with PTSD and BPD. In healthy participants, a previous study demonstrated that hydrocortisone impairs declarative memory retrieval of word pairs learned 24 hours prior to cued recall. This was accompanied by a decline in parahippocampal activity during PET (De Quervain et al., 2003). This finding supports the hypotheses that the well-known reduced memory retrieval performance after stress and cortisol administration is related to reduce hippocampal activity. Yehuda and colleagues investigated Gulf War veterans using PET, and showed that hippocampal metabolic activity was increased after hydrocortisone administration compared with a placebo condition in patients with PTSD (Yehuda et al., 2010). Yehuda et al. examined male war veterans (Yehuda et al., 2010), whereas we investigated women who predominantly reported childhood trauma. As PTSD and BPD patients in the current study did not differ in PTSD symptoms (PDS-r scores), one might argue that the symptoms were not PTSD specific enough to reveal disorder-specific effects in PTSD patients as described by Yehuda and colleagues.

In accordance with our hypotheses in study three, severity of CT correlated positively with hydrocortisone-induced activation of the amPFC, vlPFC, PCC, angular gyrus, and cerebellum during AM retrieval. Thus, self-reported CT appears to be positively associated with hydrocortisone-induced activation of these brain areas. These results suggest that enhancing effects of hydrocortisone might be related to CT rather than the disorder. Previous studies have shown that hydrocortisone improved memory retrieval in patients with PTSD and BPD, in contrast to healthy participants, who showed attenuated memory retrieval (Wingenfeld et al., 2013; Wingenfeld et al., 2012). Patients in these studies reported a high rate of CT. The current study extended this research by investigating the neural underpinnings of this phenomenon. Results in human studies are in line with results in adult rodents with early-life stress experiences. These animals were characterized by reduced number of MR and GR in the hippocampus and showed impaired LTP, which was enhanced after glucocorticoid treatment

(Champagne et al., 2008). Glucocorticoid treatment, however, impaired LTP in control animals with no early-life stress experiences (Champagne et al., 2008). This prompts the question of what leads to the enhancing effect of glucocorticoids in participants with CT and of how that might relate to lower numbers of hippocampal MRs and GRs. As secondary aims were to more closely investigate the role of CT in alterations of stress-regulating systems and stress-relevant brain regions and to reveal possible mechanisms linking CT to the psychopathology of PTSD and BPD, I present possible answers to these questions in chapter 6.3., which focusses on the role of CT.

Figure 13. Glucocorticoids and memory retrieval.



Psychopathology in two possible dimensions related to depressive symptoms and trauma associated symptoms resulting in differences in HPA axis regulation and effect of exogenous cortisol on memory retrieval according to (Katja Wingenfeld, Spitzer, Rullkötter, et al., 2010). CT = Childhood trauma, AM = autobiographical memory.

6.2.4. Summary

The main findings of the current dissertation project confirm in parts previous overlapping findings in PTSD, BPD and participants with CT (see chapter 1.5 and figure 14). The main results and interpretations are as follows:

We found a blunted cortisol response and an increased subjective perceived stress response in female patients with PTSD. Measure of cortisol changes over time in response to a psychosocial stressor correlated negatively with severity of CT. Blunted cortisol responsivity might be an adaptive process to enhance CRH, which results from the effects of CT, on lower levels of the HPA axis. Contrary to our hypothesis, however, we found no evidence for

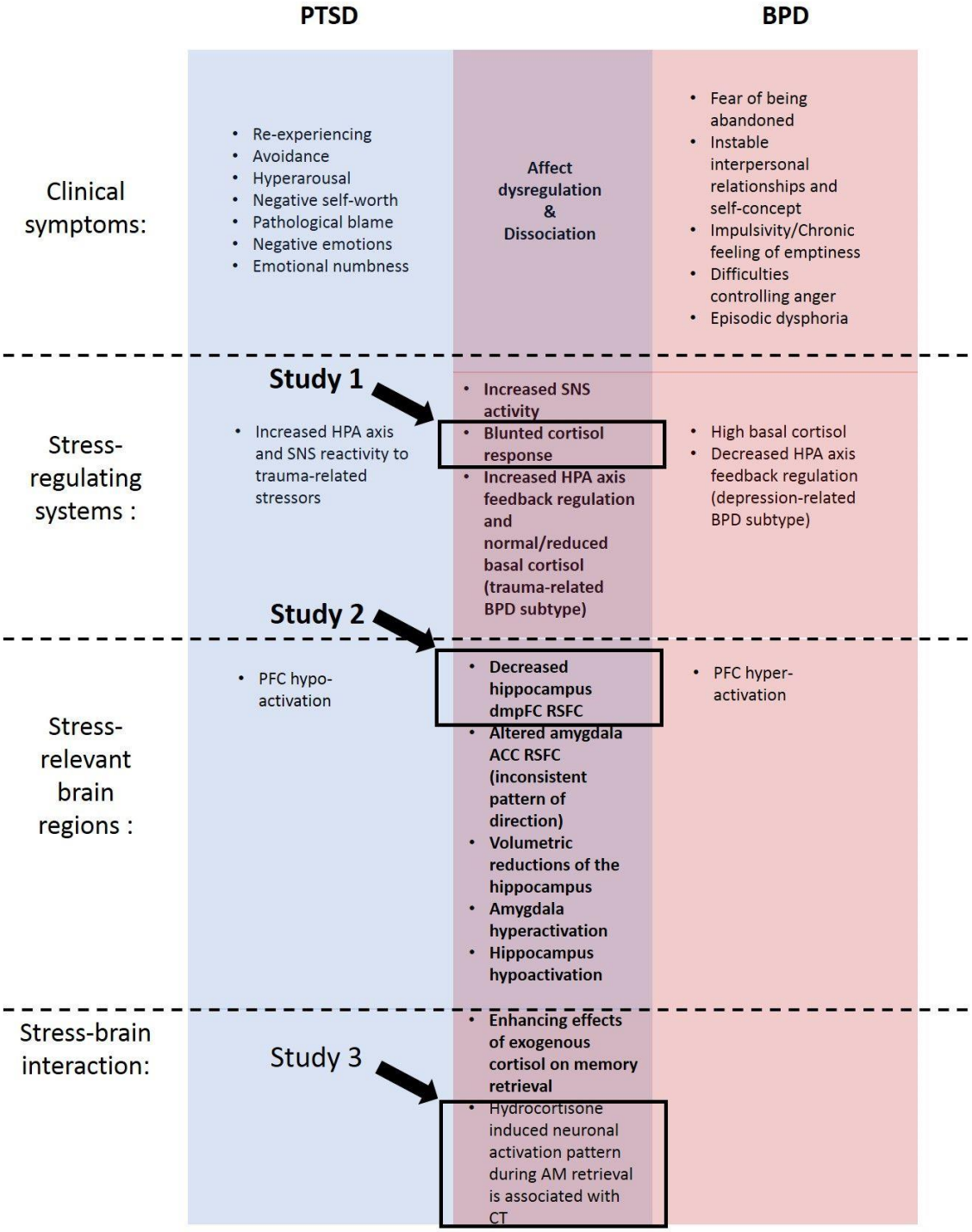
increased SNS reactivity to a psychosocial stressor. The results indicate that SNS reactivity might be especially increased in response to emotionally arousing stimuli (e.g. trauma-related stimuli) in patients with PTSD. In addition, we only partially confirmed the suggested increased basal SNS activity in patients with PTSD, BPD and participants with CT, finding a trend for increased diastolic blood pressures but no differences in systolic blood pressure and sAA in patients with PTSD.

Compared with healthy women, female patients with PTSD and BPD showed reduced hippocampus dmPFC RSFC which correlated negatively with severity of CT and with severity of clinical symptoms. CT might lead to decreased hippocampus dmPFC RSFC. Results are in line with a proposed smaller and hypoactive hippocampus in patients with PTSD and BPD and in participants with CT. This might explain symptoms of PTSD and BPD, which are characterized by dysfunctional fear regulation, as the hippocampus mPFC interaction has been shown to be relevant for fear regulation. We found no differences in amygdala RSFC, contradicting former findings showing a hyperactive amygdala with disrupted ACC RSFC in both patient groups and participants with CT. This is in line with the missing effects on SNS noted in study one, and with the proposed need of emotionally arousing material to reveal differences. In addition, no effect of hydrocortisone administration was found during resting state.

CT correlated positively with hydrocortisone effects on neural activity in AM related brain regions. These results suggest that in participants with CT, hydrocortisone has enhancing effects on neural activity during AM retrieval, while effects of hydrocortisone are rather deteriorating in healthy participants without CT (see figure 12 for summary of results). This confirms the findings of previous behavioral and animal studies demonstrating an enhancing effect of glucocorticoids in participants with CT. Patients with PTSD and BPD did not differ in their neural activity during AM retrieval in either the placebo condition or after hydrocortisone administration, suggesting that the enhancing effect of hydrocortisone, shown in former studies, might be predominantly related to CT rather than the diagnosis per se.

Figure 14 depicts the results of study one, two and three in the light of the existing body of literature.

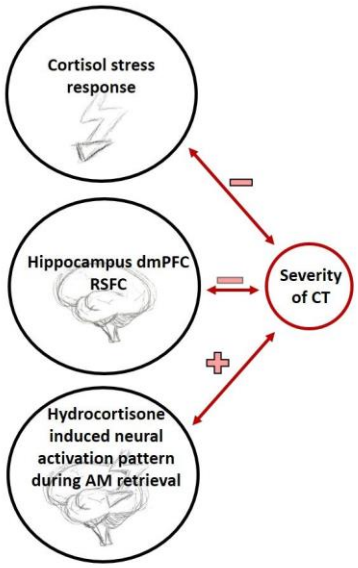
Figure 14. Results of study one, two and three in the light of the existing body of literature.



For depiction, the results of study three are shown as overlapping feature. SNS = Sympathetic nervous system, HPA axis = Hypothalamic-pituitary-adrenal axis, GR = Glucocorticoid receptor, PTSD = Posttraumatic Stress Disorder, BPD = Borderline Personality Disorder, PFC = Prefrontal cortex, ACC = Anterior cingulate cortex, RSFC = Resting state functional connectivity, dmPFC = Dorsomedial prefrontal cortex, AM = Autobiographical memory.

All three studies, which aimed at further characterizing overlapping and distinct features in stress-regulating systems and stress-relevant brain regions in patients with PTSD and BPD, have demonstrated an association with CT (see figure 15).

Figure 15. The role of CT.



CT = Childhood trauma, dmPFC = Dorsomedial prefrontal cortex, RSFC = Resting state functional connectivity, AM = Autobiographical memory.

The next chapter, therefore, focusses on the role of CT as a factor explaining the overlapping features in stress-regulating systems and stress-relevant brain regions.

6.3. Integration of the results - a hypothetical model linking CT to the psychopathology of PTSD and BPD

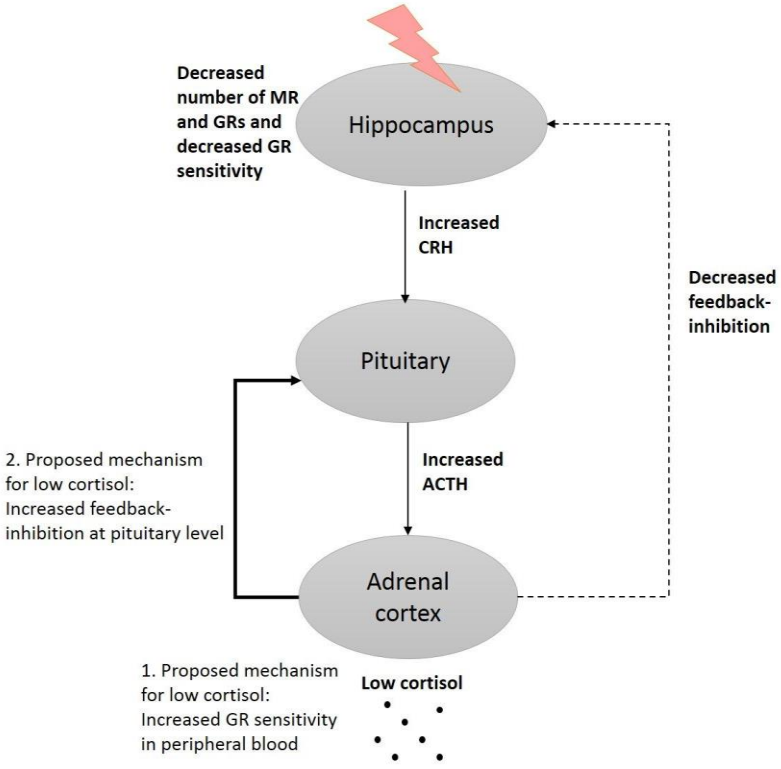
The current dissertation project revealed a blunted cortisol stress response, decreased hippocampus dmPFC RSFC and a hydrocortisone induced pattern of neural activity in relation to CT. The following mechanisms, focusing on GR expression, are proposed to merge the current findings and to link CT with the psychopathology of PTSD and BPD:

Firstly, an influence of CT or low maternal care on MR and GR expression in the hippocampus has been suggested by previous studies (Champagne et al., 2008; McGowan et al., 2009). Turecki and Meaney proposed increased methylation of the GR promoter (part of the GR gene regulating gene expression) in relation to early life adversity and parental stress as a possible cause of decreased GR expression (Turecki & Meaney, 2016). Accordingly, reduced levels of GR expression and increased methylation of the GR promoter in the hippocampus in abused suicide victims have been shown (McGowan et al., 2009). This echoes results in adult rodents with early-life stress experiences, who show a reduced number of MR and GR in the hippocampus (Champagne et al., 2008). Studies, therefore, suggest increased promotor methylation and decreased hippocampal MR and GR expression in participants with CT. However, decreased GR (and MR) expression have several possible consequences which may explain the results of the current dissertation project.

First, activation of hippocampal GR decreases HPA axis activity. Accordingly, increased CRH activity preceding increased ACTH due to missing inhibitory feedback by hippocampal GR might be related to CT (see figure 16) (Heim & Nemeroff, 2001). Therefore, an increase in pituitary ACTH in response to stress in participants with CT is in line with decreased hippocampal GR expression (Heim et al., 2002). As stated above, blunted cortisol increase following a psychosocial stressor in female patients with PTSD and in relation to CT in study one of this dissertation project (Metz et al., 2020) might be adaptation processes to enhanced CRH. Accordingly, Labonté and colleagues revealed lower morning cortisol release, higher GR messenger ribonucleic acid (mRNA) expression and lower overall methylation levels in GR promoters in peripheral blood. The authors assume that lower levels of cortisol are the consequence of peripheral GR hypersensitivity (Labonte et al., 2014). However, it has also been proposed that enhanced pituitary feedback is a possible mechanism explaining a low cortisol stress response (Fries, Hesse, Hellhammer, & Hellhammer, 2005). Taken together, decreased central GR expression leads to enhanced CRH with low cortisol as an adaptive mechanism occurring at lower levels of the HPA axis. Whether low cortisol results from enhanced GR sensitivity in peripheral blood cells or from enhanced pituitary feedback is still a matter of debate.

See figure 16 for proposed possible mechanism.

Figure 16. HPA axis reactivity after stress in participants with CT.



Schematic representation of the activation of the HPA axis in participants with CT. MR = Mineralocorticoid receptor, GR = Glucocorticoid receptor, CRH = Corticotropin-releasing-hormone, ATCH = Adrenocorticotrophic hormone.

A blunted cortisol stress response has several subsequent consequences. It first serves to protect the organism from the damaging effects of increased elevated glucocorticoid levels, which may result in heightened allostatic load associated with higher mortality (Fries et al., 2005). Furthermore, it has been suggested that low cortisol may promote SNS activity that enables adaptation to stressful situations, e.g. increased arousal (Raison & Miller, 2003). Although we found no evidence for increased SNS reactivity (see chapter 6.2.1.), there is initial evidence that blunted cortisol levels might contribute to increased catecholamine output due to missing inhibitory effects of glucocorticoids on CRH release and consequently on adrenergic system activation (see chapter 1.2. for further details on interaction of CRH and adrenergic system) (Zoladz & Diamond, 2013). In addition, a mood-buffering effect of cortisol has been suggested (Het et al., 2012; Het & Wolf, 2007). Accordingly, a blunted cortisol response following stress exposure results in worse mood and more dissociative symptoms. (Metz et al., 2020). Taken together, low basal and stimulated cortisol as a possible consequence of enhanced CRH and decreased central GR expression may result in increased adrenergic activity and in increased negative mood and high dissociation following stress.

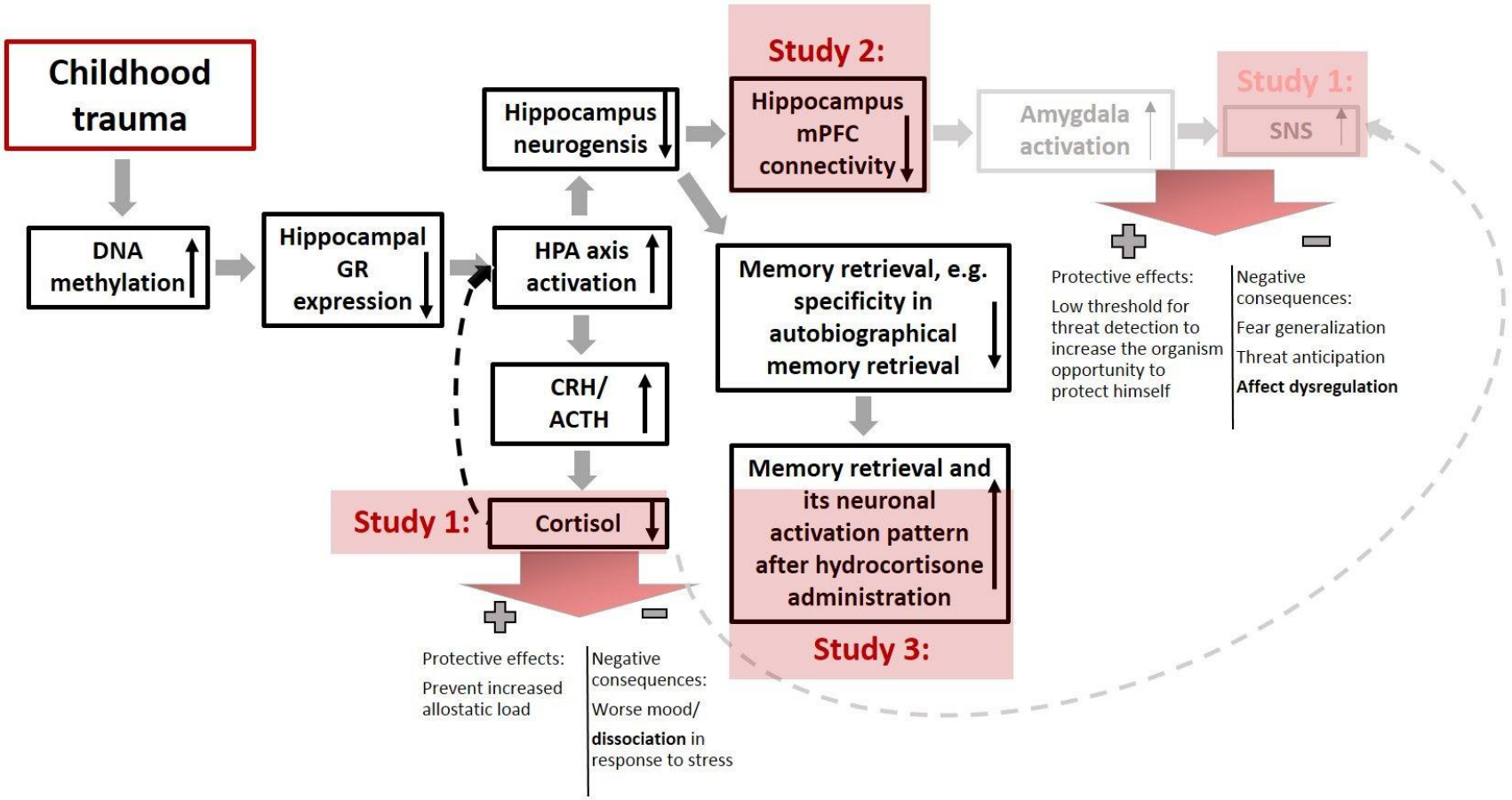
Secondly, decreased hippocampal GR (and MR) expression and high level of glucocorticoids due to a stressful environment in early life may attenuate hippocampus neurogenesis (Daskalakis, De Kloet, Yehuda, Malaspina, & Kranz, 2015; Lupien et al., 2009; Oitzl et al., 2010). Low MR and GR density and high levels of glucocorticoids might decrease brain derived neurotrophic factor (BDNF) (Meaney, 2001). Particularly during early life, high BDNF and low glucocorticoid levels enable neuronal maintenance, synaptic integrity and dendritic spine stabilization (Daskalakis et al., 2015). Since the hippocampus volume dramatically increases during the first two years of life (Lupien et al., 2009), elevated levels of glucocorticoids and low MR and GR expression during this period may have drastic consequences on hippocampus development. This hypothesis is in line with a smaller and hypoactive hippocampus in patients with PTSD and BPD and participants with CT (Doll et al., 2013; Juengling et al., 2003; Lecei & van Winkel, 2020; Shin et al., 2006; Teicher, Anderson, & Polcari, 2012; Wingenfeld, et al., 2010). The results of the second study of this dissertation project hint toward a disrupted hippocampus RSFC, which is again in line with disrupted hippocampal neurogenesis in these patients. Decreased hippocampus dmPFC RSFC in patients with PTSD and BPD correlated negatively with severity of CT and clinical symptoms (Metz, et al., 2019). As both brain regions have been implicated in amygdala inhibition (Marek et al., 2018), it has been proposed that decreased hippocampus activity and amygdala hyperactivation are consequences of CT (Lecei & van Winkel, 2020). This increases fear-generalization and

threat-anticipation and interpretation (Lecei & van Winkel, 2020). Increased amygdala reactivity may also result in increased catecholamine-mediated responses in subjects with CT (Otte et al., 2005; Taylor, 2010). This is in line with increased SNS activity in patients with PTSD, BPD or participants with CT (Barber et al., 2019; Eddie et al., 2018; Heim et al., 2000; Otte et al., 2005; Wingenfeld et al., 2015). Results of study one of the current dissertation project revealed a trend for increased basal diastolic blood pressure, irrespective of stress induction in patients with PTSD, but could only partially confirm heightened SNS activity, as no differences in systolic blood pressure and sAA could be found. Moreover, we found no association of SNS activity with CT (Metz et al., 2020). However, heightened amygdala activation and basal SNS activity in patients with PTSD and BPD and in participants with CT, which have been previously reported (especially in response to emotionally arousing material), may have been adaptive in early life to decrease the threshold for threat perception in an unstable environment (Raison & Miller, 2003). Whereas, such changes may be dysfunctional in a safe and stable environment in adulthood, and result in symptoms as hyperarousal and emotional dysregulation (Kamphausen et al., 2013; Norrholm & Jovanovic, 2018).

Thirdly, the results of the third study revealed that hydrocortisone induced neural activity during AM retrieval correlated positively with severity of CT (Metz et al., 2019). These results can again be explained by reduced central GR expression in the hippocampus in participants with CT. It has been suggested that the relationship between glucocorticoids and learning is best described by an inverted U-shape (De Quervain et al., 2017; Mateo, 2008), with impaired learning occurring at very low and very high levels of glucocorticoids. Similar results have been suggested for memory retrieval (Domes, Rothfischer, Reichwald, & Hautzinger, 2005; Schilling et al., 2013). This results in optimal retrieval at intermediate glucocorticoid levels with high MR and low GR activation (Rimmele, Besedovsky, Lange, & Born, 2013). In participants with CT, an insufficient number of GR and MR activation due to decreased GR (and MR) expression might be present. Hydrocortisone administration might thus restore MR/GR balance in participants with CT, but induce imbalance in healthy participants without CT. However, studies in humans have only shown altered GR expression in the hippocampus. Our results in study three suggest altered neural activity following hydrocortisone administration outside the hippocampus: in the amPFC, the vlPFC, PCC, angular gyrus, and cerebellum. GR and MR expression in these brain regions await to be determined.

Figure 17 depicts the proposed hypothetical model in brief.

Figure 17. A hypothetical model: Effects of childhood trauma.



Schematic representation of a cascade of consequence of childhood trauma initiated by GR promotor methylation. Dashed lines represent disrupted feedback loops. Light grey figures represent results, which were not or only in part supported by the results of the current dissertation project. DNA = Deoxyribonucleic acid, MR = Mineralocorticoid receptor, GR = Glucocorticoid receptor, HPA = Hypothalamic-pituitary-adrenal axis, ACTH = Adrenocorticotrophic hormone, CRH = Corticotrophin-releasing-hormone, mPFC = medial prefrontal cortex, CT = Childhood trauma, SNS = Sympathetic Nervous System.

Taken together, the model proposes that reduced central GR expression initiates a cascade which results in blunted cortisol response, disrupted hippocampus dmPFC RSFC and an enhancing effect of hydrocortisone in participants with CT. In the next chapter, I outline implications for future research and clinical practice derived from these proposed mechanisms.

6.4. Implications for future research

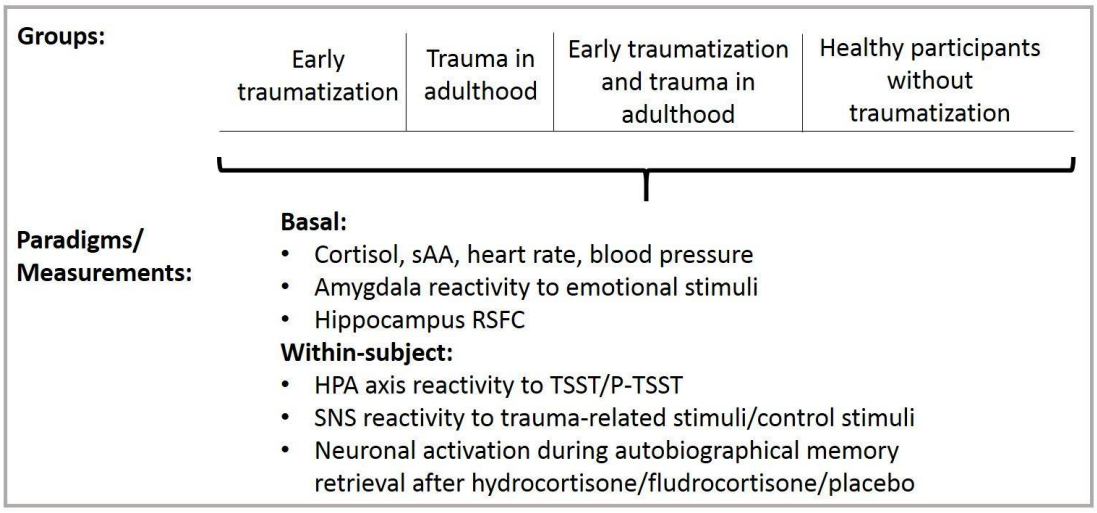
The results discussed above (chapter 6.1.1., 6.1.2.& 6.1.3) have various implications for research and for clinical practice.

As the current dissertation project only included patients with PTSD and BPD with CT and healthy participants without CT, future studies should include a group with healthy participants with CT, to ascertain that effects are related to CT and to clearly disentangle them from disorder specific effects. Since patients with MDD, especially the chronic form with an early onset report a high rate of CT (Nelson, Klumparendt, Doebler, & Ehring, 2017), differences and similarities in stress-regulating systems and stress-relevant brain regions are worthwhile investigating. Including a further group with healthy participants with CT and depressed participants with CT might help to further describe which processes lead to different phenotypes after similar environmental factors e.g. CT and might help reveal protective factor in the case of healthy participants with CT.

The majority of patients included in the current dissertation project reported CT and trauma in adulthood. One might argue that the cortisol response is all the more blunted, if further traumatization takes place in later life as it further activates the central HPA axis and necessitates further adaptation on lower levels of the HPA axis. However, hippocampal neurogenesis seems to be especially attenuated in response to stress during the first years of development (Lupien et al., 2009). These results suggest that the findings of this dissertation project arise from a combination of early traumatization (resulting in disrupted hippocampus RSFC) and further traumatization in adulthood (resulting in low cortisol). Future studies should further differentiate these effects in patients with PTSD and BPD by including different groups. For example, within patients with PTSD, one could include a group with early trauma and no further traumatization in adulthood, one group with only trauma in adulthood, one group with participants who experienced both and a control group with healthy participants with no traumatization. All four groups should undergo the paradigms and measurements described in study one, two and three of this dissertation project (see figure 18). As most studies have described an association of low cortisol and CT (Meewisse et al., 2007), it would be interesting

to test whether the results of study one can also be found in participants with no early traumatization and only trauma in adulthood. One might suggest that participants with trauma in adulthood show no central decreased GR and MR expression and therefore no increased CRH and ACTH secretion. It would be interesting to see whether adaptive process on lower levels of the HPA axis still occur following a traumatic event during adulthood, due to high cortisol levels during trauma. To further confirm the proposed central role of the GR in the current dissertation project, I would additionally administer fludrocortisone (see figure 18). In human studies, only the GR has been shown to be downregulated in the hippocampus of participants with CT (McGowan et al., 2009). Although there is some evidence from animal studies that different brain regions may be affected (Avishai-Eliner, Hatalski, Tabachnik, Eghbal-Ahmadi, & Baram, 1999) and that the MR is downregulated in the hippocampus in rodents with low maternal care (Champagne et al., 2008), little is known about these effects in humans. If results of study three could not be found after fludrocortisone administration, it would further confirm the proposed central role of the GR in the current dissertation project. I would additionally include an emotional paradigm to investigate amygdala reactivity and a paradigm that investigates the stress response to trauma-related stimuli to confirm the suggested amygdala and SNS hyperactivity in participants with CT.

Figure 18. Research design for a possible future study in patients with PTSD.



Schematic representation of a possible future research design. sAA = salivary alpha amylase, RSFC = resting state functional connectivity, HPA axis = Hypothalamus-pituitary-adrenal axis, SNS = Sympathetic nervous system, TSST = Trier social stress test, P-TSST = Placebo TSST.

Despite the fact that central GR expression is difficult to investigate, the relationship between central and peripheral GR expression and sensitivity - especially in relation to CT versus trauma during adulthood - seems to be under-investigated and thus requires further

investigation. Reduced GR central expression in the hippocampus in participants with CT (McGowan et al., 2009) and increased GR expression and binding in peripheral blood in patient with PTSD have been described (Yehuda et al., 2004). These differences might be either tissue specific effects or due to changes over time (first downregulation than hypersensitivity). Longitudinal studies could test whether the results are time and tissue specific and ascertain causal direction. Furthermore, timing of stress induction seems to be highly relevant not only to the memory domain to disentangle faster non-genomic and slower genomic effects of glucocorticoids and should be further investigated (Shields, 2020). Similarly, methods of stress induction, differentially activating the HPA axis and the SNS require further investigation (Giles, Mahoney, Brunyé, Taylor, & Kanarek, 2014; McRae et al., 2006).

Considering implications for clinical practice, affect dysregulation and dissociation seem to characterize early and chronically traumatized individuals. Affect dysregulation has also been described to predict subsequent dissociation (Powers et al., 2015). Therefore, affect dysregulation would seem to present a good target in participants with early and chronic CT that can be well addressed by psychotherapy. Accordingly, psychotherapeutic concepts designed for patients with early and chronic CT focusing on affect regulation as the Skills Training in Affective and Interpersonal Regulation (STAIR concept) by Marylene Cloitre (Schäfer, Borowski, & Cloitre, 2019), are very promising. This concept aims at improving emotion regulation based on cognitive, bodily and behavioral strategies, in addition to acceptance and understanding of emotional experiences. Psychotherapy, which focusses on emotion regulation, awareness and understanding of emotional experiences might help individuals with CT understand how their emotional perception (e.g. hyperreactive fear response) might highly contribute to interpersonal difficulties. Psychotherapy in general might help patients devise new strategies to deal with altered emotional perception, and to undertake new experiences which enable them to better dissociate safe from threatening environments.

Taken together, the findings discussed above have promising implications for future research. The above described hypothetical model, encompassing the results of study one, two and three, proposes mechanisms which represent possible targets for psychotherapeutic and psychopharmacological treatments and should therefore be further investigated in different samples (e.g. with different timing of traumatization).

6.5. Conclusion

The main aim of this dissertation project was to shed further light on overlapping and distinct features of PTSD and BPD in stress-regulating systems, stress-relevant brain regions and their

interplay to further explain the evolvement of symptoms such as affect dysregulation and dissociation. As a secondary aim, the role of CT as one factor explaining variance in especially overlapping features was examined. To do so, the present dissertation project first outlined overlapping und distinct symptoms, features of stress-regulating systems, stress-relevant brain regions and their interplay in both disorder and the relevance of CT to these changes (chapter 1). In addition, I examined the three following research questions to further characterize overlapping and distinct features in PTSD and BPD and the role of CT. *Firstly, how do female patients with PTSD differ in their physiological and subjectively perceived stress response to an acute psychosocial stressor, compared with healthy women, and how do these differences relate to CT? (chapter 3)?* The results revealed that female patients with PTSD were characterized by a blunted cortisol stress response. In addition, measure of cortisol changes over time in response to a psychosocial stressor correlated negatively with severity of CT. Furthermore, we found a trend for basal increased diastolic blood pressure, but no evidence for increased basal systolic blood pressure and basal sAA or heightened SNS stress reactivity (Metz et al., 2020). *Secondly, how does amygdala and hippocampus RSFC differ between female patients with PTSD and BPD and healthy women, in a placebo condition and after hydrocortisone administration, and how does amygdala or hippocampus RSFC in the placebo or hydrocortisone condition relate to CT (chapter 4)?* Results revealed that hippocampus dmPFC RSFC, which correlated negatively with severity of CT and clinical symptoms, was reduced in patients with PTSD and BPD. We found no differences in amygdala RSFC, nor did we find a main effect of hydrocortisone administration, nor an interaction of hydrocortisone with group on either amygdala or hippocampus RSFC (Metz et al., 2019). *Thirdly, how do female patients with PTSD and BPD differ from healthy women in their neural activity during AM retrieval after hydrocortisone administration compared with a placebo condition, and how do these differences relate to CT (chapter5)?* Female patients with PTSD and BPD and healthy women did not differ in their neural activity during AM retrieval neither in the placebo condition, nor after hydrocortisone administration. Severity of CT correlated with a hydrocortisone-induced pattern of neural activity during AM retrieval (Metz et al., 2019).

To conclude, the conducted studies extend findings on stress-regulating systems, stress-relevant brain regions and their interplay in patients with PTSD and BPD and reveal an association with CT. Hence, the developed hypothetical model describes how CT constitutes a risk factor for psychiatric disorders. The proposed hypothetical model assumes that CT might lead to decreased hippocampal GR expression. Accordingly, decreased GR (and MR) expression might attenuate hippocampus neurogenesis and thereby lead to a disrupted

hippocampus dmPFC RSFC. This in turn attenuates amygdala inhibition and leads to high SNS activity, protective for the organism under high stress conditions in early life due to low threshold for threat perception, however, leading to affect dysregulation in adulthood. Second, decreased hippocampal GR expression might induce central HPA axis hyperreactivity due to missing inhibitory feedback, resulting in enhanced CRH. Low basal and stress dependent cortisol levels might be an adaptation to centrally increased CRH, occurring at a lower level of the HPA axis to decrease allostatic load. This, however, might attenuate the mood buffering effect of cortisol, possibly explaining dissociation in adulthood under high stress conditions. Furthermore, an imbalance of MR/GR activation due to decreased GR (and MR) expression in the brain might attenuate memory process. Hydrocortisone might normalize ratio of MR and GR activation and therefore neural activity in participants with CT, while it disrupts ratio of MR/GR activation and therefore neural activity in healthy participants without CT.

Overall, the current dissertation project described a pivotal role of early experiences in the development of stress-regulating systems and stress-relevant brain regions. Affect dysregulation and dissociation resulting in difficulties in interpersonal situations affecting occupational and social situations represent possible consequences of CT.

Therefore, this dissertation project emphasizes the importance of an early stable environment for the development of a stress response and affect regulation that is adaptive and well-functioning throughout the lifespan, and thus enables engagement in satisfying interpersonal situations.

7. References

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8. Appendix

List of Figures

List of Abbreviations

AA = Alpha amylase.

ACC = Anterior cingulate cortex.

ACTH = Adrenocorticotrophic hormone.

AM = Autobiographical memory.

AMT = Autobiographical memory test

BNDF = Brain-derived neurotrophic factor.

BOLD = Blood oxygen level dependent.

BPD = Borderline personality disorder.

BSL = Borderline symptom list.

CNS = Central nervous system

CRH = Corticotrophin-releasing-hormone.

CT = Childhood trauma.

CTQ = Childhood trauma questionnaire.

dmPFC = dorsomedial prefrontal cortex.

DSM = Diagnostic and Statistical Manual of Mental Disorders.

GR = Glucocorticoid receptor.

HPA = Hypothalamic-pituitary-adrenal.

HRV = Heart rate variability.

LC = Locus coreolus.

LTP = Long term potentiation.

MDD = Major depressive disorder.

mPFC = Medial prefrontal cortex.

MR = Mineralocorticoid receptor.

mRNA = Messenger ribonucleic acid.

OFC = Orbitofrontal cortex.

PCC = Posterior cingulate cortex.

PDS-r = Posttraumatic stress diagnostic scale.

PET = Positron emission tomography.

PFC = Prefrontal cortex.

PTSD = Posttraumatic stress disorder.

P-TSST = Placebo TSST.

RSFC = Resting state functional connectivity.

sAA = Salivary alpha amylase.

SCID = Structured Clinical Interview for DSM.

SNS = Sympathetic nervous system.

TSST = Trier social stress test.

vmPFC = ventromedial prefrontal cortex.

Supplementary Material – Study 1: Psychophysiological stress response in PTSD

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Supplementary Material – Study 3: Effects of hydrocortisone on autobiographical memory retrieval in PTSD and BPD

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Eidesstattliche Versicherung (statement of authorship)

Ich versichere, dass ich die vorgelegte Arbeit selbstständig und ohne unerlaubte Hilfe angefertigt habe. Ich habe die vorliegende Dissertation an keiner anderen Universität eingereicht und besitze keinen Doktorgrad im Fach Psychologie. Die Promotionsordnung der Freien Universität Berlin vom 08.08.2016 (FU-Mitteilung 35/2016) ist mir bekannt.

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