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Endocrinological Alterations in Adolescent Self-Harm and Borderline Personality Disorder

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‘In physiology, as in all other sciences, no discovery is useless, no curiosity misplaced or too ambitious, and we may be certain that every advance achieved in the quest of pure knowledge will sooner or later play its part in the service of man.’

- Sir Ernest Henry Starling

Sir Ernest Henry Starling (1866 – 1927) introduced the term ‘hormone’ adapted from the Greek verb ‘to excite or arouse’ (ormao). The discovery of hormones and the further understanding that they were carried by the bloodstream to the organ affected revolutionized physiology and provided the foundation for endocrinology as a medical discipline. Sir Starlings research has been influenced heavily by his collaboration with Wilhelm Friedrich Kühne in Heidelberg.

Abstract

Borderline personality disorder (BPD) has its onset in adolescence or early adulthood and is frequently accompanied by nonsuicidal self-injury (NSSI), which is a common phenomenon in adolescence and may be viewed as a disorder in its own right. While BPD has been studied extensively in the past decades, NSSI has just recently been added as a condition for further study to the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2013). For BPD, Linehan (1993) postulated based on her biosocial theory that emotion dysregulation arises from interactions between biological vulnerabilities and environmental influences. Put differently, Linehan claimed that adverse childhood experiences aggravate biological stress responses and vice versa. Biological stress responses are for instance mirrored by aberrant endocrinological functioning. The biosocial theory has been extended by Crowell et al. (2009) to focus on developmental psychopathology and trait impulsivity in BPD. For NSSI, a temporal framework has recently been proposed by Kaess et al. (2021) to distinguish relevant traits (proximal biological correlates and distal risk factors) and states (biological mechanisms before, during or after NSSI incidents) underlying NSSI. Based on this categorization, the temporal framework aims at differentiating mechanisms and risk factors underlying behaviors, cognitions, and emotions characteristic for NSSI.

The current dissertation evaluated both theoretical approaches with regard to development and maintenance of BPD and NSSI by focusing on endocrinological markers of the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-thyroid (HPT) axes. These endocrinological axes were investigated as they may mirror stress responses adequately and as corresponding imbalances have been interpreted as warning signs for the development of several psychopathologies. According to this, a meta-analysis was performed in **Study 1** to systematically investigate altered HPA axis functioning in BPD patients. Adult BPD patients were compared to healthy and clinical controls based on several experimental paradigms. Findings indicated blunted cortisol responses to psychosocial stressors and elevated continuous cortisol in BPD patients. To examine endocrine concomitants of development and aging in BPD more closely, **Study 2** focused on the so-called cortisol awakening response (CAR) in female adolescents and adults with BPD compared to healthy controls. Here, findings showed increased CARs in BPD patients. Positive correlations between age and CAR in BPD patients further suggested that endocrine alterations may amplify with increasing age and chronification of the disorder. To expand the empirical evidence for endocrine markers in BPD

and NSSI, **Study 3** focused on HPT axis markers and cortisol in adolescents with NSSI and showing a variable number of BPD symptoms. In addition to cortisol, thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), and the ratio of these hormones (fT3/fT4 ratio) were examined and compared to markers obtained from healthy adolescents. Endocrine markers were further correlated with focal psychopathological measures to allow for a dimensional perspective on biological stress responses in NSSI patients. Here, altered HPT axis functioning in NSSI patients showed through lower fT3/fT4 ratio values. Besides, negative correlations between fT3, fT3/fT4 ratio and severity of BPD symptoms, depression scores and symptomatic distress were observed. Lastly, TSH correlated negatively with severity of BPD symptoms and symptomatic distress.

In brief, the current dissertation affirms several premises of the biosocial theory for BPD and the temporal framework for NSSI by showing that altered endocrinological functioning depends on several factors such as developmental psychopathology and symptom severity. Yet, findings also suggest that more research on potential mediators, such as adverse childhood experiences, is needed before endocrinological markers can be used to implement and evaluate personalized treatments. Nonetheless, the current dissertation contributes to a comprehensive characterization of HPA and HPT axis markers in BPD and NSSI patients, which is why these markers may eventually be used as reliable and change-sensitive measurements in future therapy research and clinical practice.

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List of Scientific Publications for the Publication-Based Thesis

First Manuscript

Drews, E., Fertuck, E. A., Koenig, J., Kaess, M., & Arntz, A. (2019). Hypothalamic-Pituitary-Adrenal Axis Functioning in Borderline Personality Disorder: A Meta-Analysis. *Neuroscience & Biobehavioral Reviews*, *96*, 316-334. https://doi.org/10.1016/j.neubiorev.2018.11.008

Second Manuscript

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Third Manuscript

Flach, E., Koenig, J., van der Venne, P., Parzer, P., Resch, F., & Kaess, M. (2021). Hypothalamic-Pituitary-Thyroid Axis Function in Female Adolescent Nonsuicidal Self-Injury and its Association with Comorbid Borderline Personality Disorder and Depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 111,* 110345. https://doi.org/10.1016/j.pnpbp.2021.110345

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On the Origins of BPD and NSSI – A Developmental Perspective

Interactions between psychopathological characteristics, acute and chronic stressors, and endocrinological markers seem to play a pivotal role for development of borderline personality disorder (BPD) and nonsuicidal self-injury (NSSI). According to existing evidence, adolescence deserves special mention because of the related brain maturation processes and crucial changes in enzymatic activity. As hormonal sensitivity to neurotoxic and neuroprotective effects of stress seems to be particularly pronounced during adolescence and young adulthood (Kamin & Kertes, 2017), psychopathological characteristics, central etiological theories, and the current state of clinical research on BPD and NSSI with an emphasis on adolescence will be presented in the following.

Borderline Personality Disorder – Characteristics, Theory, and Clinical Research

BPD is a highly debilitating mental disorder. As shown in **Table 1**, characteristic symptoms include affective instability, impulsivity, interpersonal difficulties and unstable self-image (APA, 2013). By definition, symptoms must be pervasive, persistent and pathological to justify the corresponding diagnosis. First warning signs in adolescence and early adulthood encompass impulsive or risk-taking behaviors, repetitive NSSI, and suicide attempts. BPD has gained increased attention in the past decades due to its association with elevated suicide risk, extensive mental health service use, impaired psychosocial functioning, and high social and economic costs (Leichsenring et al., 2011). In the general population, BPD is most prevalent in adolescents and young adults, with a cumulative prevalence ranging from 3.2% - 5.9% (Zanarini et al., 2011). Research on adolescent outpatient settings further indicates a prevalence of 11% (Grilo et al., 1996). For adolescent inpatient settings, a prevalence up to 50% has been reported (Chanen et al., 2008a). So taken together, BPD can be considered a serious, albeit relatively common mental disorder, which usually manifests in adolescence and young adulthood.

Table 1

Diagnostic Criteria for Borderline Personality Disorder (301.83) According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA, 2013)

A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

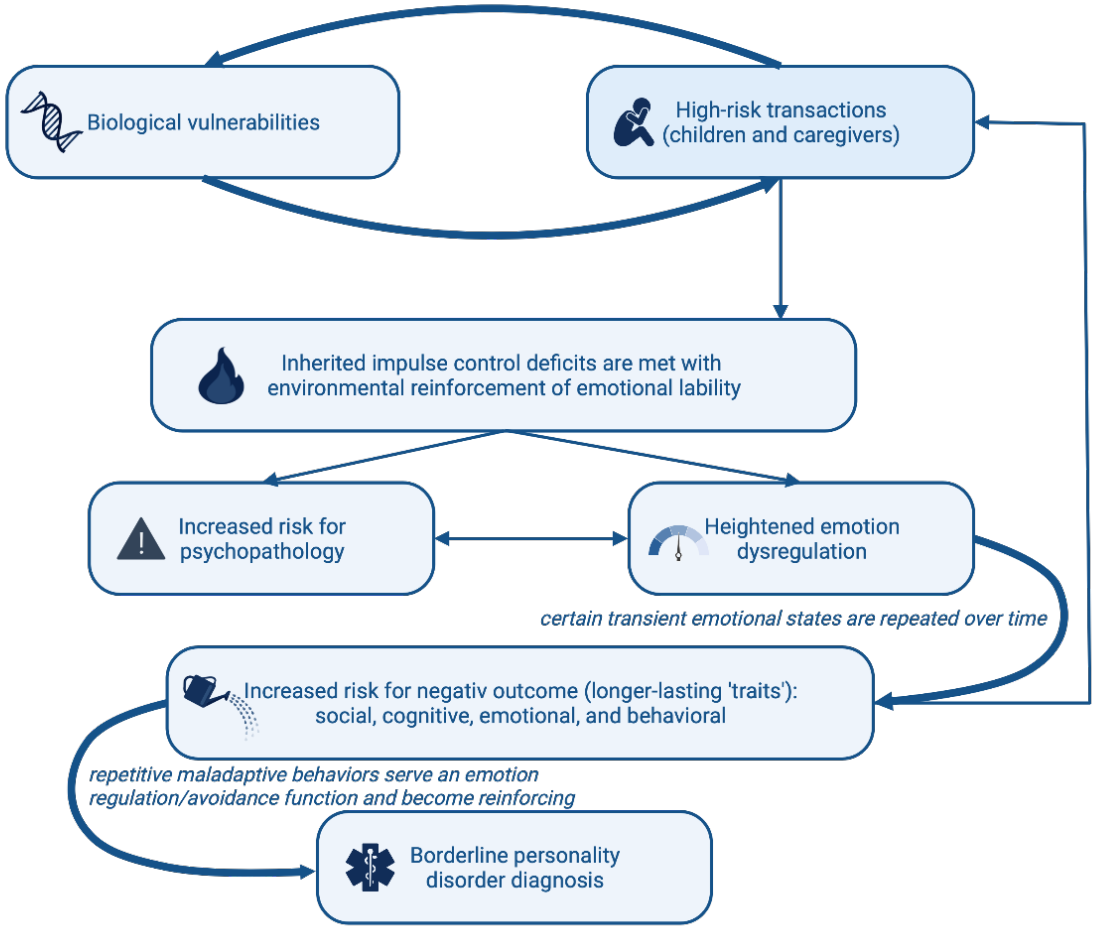
1. Frantic efforts to avoid real or imagined abandonment (**Note:** Do not include suicidal or self-mutilating behavior covered in *Criterion 5*.)
2. A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization or devaluation.
3. Identity disturbance: markedly and persistently unstable self-image or sense of self.
4. Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating). (**Note:** Do not include suicidal or self-mutilating behavior covered in *Criterion 5*.)
5. Recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior.
6. Affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days).
7. Chronic feelings of emptiness.
8. Inappropriate, intense anger or difficulty controlling anger (e.g. frequent displays of temper, constant anger, recurrent physical fights).
9. Transient, stress-related paranoid ideation or severe dissociative symptoms.

With regard to the theoretical background, it is generally assumed that BPD development results 'from interactions between genetic, temperamental, and environmental factors, which ultimately produce a complex clinical phenotype associated with significant morbidity and disability' (Ruocco & Carcone, 2016, p. 311). One of the most important etiological models elaborating on this hypothesis is Linehan's biosocial theory of BPD (1993). Linehan considers BPD primarily as a disorder of emotion dysregulation, which is supposed to arise from transactions between biological vulnerabilities and certain environmental influences. According to the theory, emotion dysregulation is paralleled by different biological substrates, such as limbic dysfunction, and shows through heightened emotional sensitivity, the inability to regulate intense emotional responses, and a slow return to

emotional baseline. As illustrated in **Figure 1**, emotion dysregulation encompasses emotion-linked cognitive processes, biochemical and physiological processes such as facial and muscle reactions, action urges, as well as emotion-linked actions. With regard to environmental influences, Linehan hypothesized that BPD development occurs within an invalidating developmental context, for instance when caregivers do not tolerate the expression of strong emotions by their children. Consequently, Linehan assumed that children are neither taught how to modulate emotional arousal nor to cope with distress. The impact of the theory is further reflected by the fact that the corresponding treatment, dialectical behavioral therapy, is among the most established treatment methods for BPD. However, since the Linehan initially did not take trait impulsivity independent of emotion into account, Crowell et al. (2009) extended the biosocial theory by taking a life span developmental perspective. Hence, the emergence of problems during adolescence and their continuity throughout adult development are emphasized. According to the extended biosocial theory, BPD is viewed as an outcome of multiple interacting risk factors, causal events and dynamic processes. However, and despite the popularity of the biosocial theory, its underlying hypotheses on biological markers of emotion dysregulation have not been investigated sufficiently yet.

Figure 1

Adapted Biosocial Developmental Model of Borderline Personality as Developed by Linehan (1993) and Conceptualized by Crowell et al. (2009).



Note. The adapted biosocial developmental model proposes that the interplay between several factors leads to the emergence of borderline personality disorder (BPD). Here, *biological vulnerabilities* refer to (1) genetic influences, (2) abnormalities of the brain system, (3) frontolimbic dysfunction and (4) low respiratory sinus arrhythmia. Within *high-risk transactions*, typical caregiver contributions include invalidation of child emotions and inadequate coaching of emotions, negative reinforcement of aversive emotional expressions, ineffective parenting due to poorness of fit, and insufficient resources with regard to time, money and social support. Typical child contributions include negative affectivity, impulsivity, and high emotional sensitivity. According to the model, stress emerges through accumulation of high-risk transactions and corresponding reinforcement of biological vulnerabilities. *Heightened emotion dysregulation* involves several reactions to emotional situations: (1) distorted emotion processing, (2) inability to achieve non-mood-dependent

goals, (3) inability to control mood-dependent behavior, and (4) shutting down or freezing. Reactions to emotional situations are repeated over time and thereby lead to formation of *longer-lasting traits*. Here, *social* refers to social isolation, dysfunctional peer relationships or ineffective individuation from parents. *Cognitive* refers to low self-efficacy, self-hatred, hopelessness, disorganization and dissociation. *Emotion* refers to generalized emotional vulnerability, sadness, shame and anger. *Behavioral* refers to withdrawal, avoidance, and frequent impulsive behaviors such as self-injury. *BPD diagnoses* are made when repetitive maladaptive behaviors serve an emotion regulation/avoidance function and thereby become reinforcing.

As the biosocial developmental model postulates interactions between genetics, neurobiological and environmental factors (Stoffers-Winterling et al., 2021), the current state of research and corresponding findings will be summarized briefly in the following. First, and with regard to genetics, research suggests that 'BPD runs in families', as BPD is five times more common in first-degree relatives compared to the general population (Fall & Craig, 1998). Correspondingly, heritability estimates for BPD range from 35% - 45% (Chanen & Kaess, 2012) and it has been speculated that genetic factors may reflect an individual's vulnerability to BPD pathology, negative emotionality, and high impulsivity (Kendler et al., 2008). Second, and with regard to neurobiological research, several bodily systems and mechanisms seem to accompany BPD development (Cattane et al., 2017). Here, links between reduced serotonergic activity and impulsivity have been reported repeatedly (e.g. Ni et al., 2006). Electrophysiological studies in BPD patients further demonstrated abnormal brain electrical activity, which has been interpreted as a correlate of impulsivity and affective instability associated with the disorder (Kuo & Linehan, 2009). Structural and functional imaging studies point altered hippocampal and amygdalar structures as well as altered frontolimbic networks, which collectively suggests reduced stress regulation capacities (Leichsenring et al., 2011). Yet, neurobiological findings appear somewhat inconsistent and should therefore be interpreted with caution (Cremers et al., 2021). For adolescents with BPD in particular, studies on amygdalar and hippocampal volumes have yielded inconclusive results (Chanen et al., 2008b; Richter et al., 2014) while research using imaging techniques seems to portend volume reductions in frontolimbic areas (Goodman et al., 2014). Correspondingly, Sharp and Kim (2015) speculated that mixed or negative neurobiological findings for hippocampal and amygdalar structures can be traced back to adverse childhood

experiences of the participating adolescents. Third, several studies investigated associations between emotion dysregulation and vagal tone[1] and initial meta-analytic findings suggest a lowered resting state vagal tone as trait characteristic in BPD patients (Koenig et al., 2016). Focusing on adolescents in particular, a recent study by our group indicated that alterations of the autonomic nervous system are rather related to symptom severity than to particular symptoms, such as emotion dysregulation (Weise et al., 2020). Taken together, existing studies suggest that genetic and neurobiological factors are altered in adults and adolescents with BPD. In particular, research indicates that elevated heritability estimates, reduced serotonergic activity, alterations with regard to neuronal structures and functioning, and altered function of the autonomic nervous system denote BPD psychopathology. Yet, it is unclear whether these mechanisms are cause, effect, or epiphenomenon of BPD, which is why supplementary research on biological markers in BPD patients seems particularly important.

Importantly, there is evidence that not only biological but also environmental factors affect BPD development (Distel et al., 2011). Pathological development may be particularly influenced by adverse parenting styles and experiences of abuse as attachment-related research concluded that insecure and preoccupied attachment styles predominate in BPD patients (Barone, 2003). And, corresponding clinical (Zanarini et al., 1997) and population-based samples (Afifi et al., 2011) confirm connections between adverse childhood experiences and BPD symptoms. Prospective studies additionally emphasize the detrimental impact of several parenting variables such as maternal inconsistency and parental hostility (Carlson et al., 2009; Cohen et al., 2005; Johnson et al., 1999). Research has further shown that grossly inappropriate parental behavior, parental loss, and maternal rejection or neglect constitute serious risk factors for insecure attachment and BPD development (Levy et al., 2015). And, contrary to the long-standing hypothesis that BPD emerges in response to sexual abuse in childhood (as reviewed in Kaess et al., 2014), empirical evidence increasingly describes childhood sexual abuse as a weak and nonspecific risk factor (Fossati et al., 1999).

Research on temperamental styles further suggests that interactions between temperamental traits, such as harm avoidance and novelty seeking, as well as invalidating, overprotective environments may predict the further course of detrimental personality development (Arens et al., 2013; Fleck et al., 2021) and corresponding cross-sectional

[1] vagal tone describes the activity of the vagus nerve and refers to a fundamental component of the parasympathetic branch of the autonomic nervous system. Among others, it mirrors the variability of the heart rate associated with inhalation and exhalation.

research in adolescents aged 11 to 14 years showed that both personality traits and environmental stressors reinforce childhood borderline features (Gratz et al., 2011). To conclude, prior research indicated that adverse childhood experiences and certain temperamental styles may contribute to BPD development (Bradley et al., 2005). Yet, corresponding risk factors often share variance and are therefore probably difficult to disentangle.

Moreover, several investigations focused on BPD over the life course and it has been widely discussed whether BPD can and should be diagnosed in adolescence (Chanen & McCutcheon, 2008). As reviewed by Kaess et al. (2014), opponents of an early diagnosis questioned its validity due to several reasons. Firstly, they have argued that several BPD criteria, such as emotional instability and identity disturbance, are part of normal development in adolescence and should therefore not be pathologized. Secondly, opponents asserted that personality development continues beyond adolescence, which – by definition – precludes diagnosing BPD prematurely. And after all, opponents adduced BPD as a highly stigmatized disorder, and argued BPD diagnoses should be avoided in adolescents as a matter of principle. Yet, and based on empirical evidence, proponents of an early diagnosis have argued that symptoms usually manifest in adolescence, peak in early adulthood and decline subsequently (Arens et al., 2013; Chanen & Kaess, 2012). Correspondingly, research characterized BPD in early adolescence in particular by pronounced risk-taking, frequent self-harm, high burden due to comorbidity, and marked psychosocial impairment (Kaess et al., 2014). Zanarini et al. (2001) further reported an average of first clinical presentation at age 18 with a standard deviation of 5-6 years, which could point to initial manifestation of BPD at age 13. Besides, studies examining validity and reliability of BPD diagnoses in adolescents have not only shown that they are equally accurate (Miller et al., 2008) but also that BPD is commensurably stable in adolescence and adulthood (Chanen et al., 2004). In adolescence, BPD may even have incremental validity compared to other common psychiatric diagnoses (Chanen et al., 2007; Kaess et al., 2013). And eventually, empirical evidence has demonstrated beneficial effects of diagnosing (Guilé et al., 2018; Kaess et al., 2014) and treating BPD at an early stage (Chanen & McCutcheon, 2013). So taken together, even though diagnosing and treating BPD in adolescence has been discussed controversially, a comprehensive investigation of the developmental course of BPD and its precursors seems particularly important to underpin the corresponding discussion empirically.

Nonsuicidal Self-Injury – Characteristics, Theory, and Clinical Research

Nonsuicidal self-injury (NSSI) has been defined as the intentional, self-inflicted damage to the surface of one's body on five or more days within a year (APA, 2013). The most common NSSI methods include cutting or carving oneself with a sharp implement, such as a knife or razor, on arms, legs or stomach. Initial research conceptualized NSSI as an independent syndrome called deliberate self-harm (Pattison & Kahan, 1983) and characterized this syndrome by harm inflicted upon the body deliberately, initiation in late adolescence, recurrent episodes, low lethality, and continuation of the behavior over many years[2]. As clinical characteristics of deliberate self-harm were assumed to be significantly different from other types of self-destructive behavior, it has further been argued that self-harm should be recorded as an independent diagnosis. Yet, it took another 30 years to officially include NSSI as formal diagnosis to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; American Psychiatric Association [APA], 2013) as shown in **Table 2.** Similarly, the *International Statistical Classification of Diseases and Related Health Problems* (11th ed., ICD-11, World Health Organization, 2019) either defines NSSI as a BPD symptom or as "intentional self-harm" (PB80-PD3Z), whereby the particular type of self-harm is specified based on categories such as 'exposure to objects' (i.e., projectiles from firearms, knifes or sharp glass).

To date, different studies focused on validating the proposed DSM-5 diagnostic criteria for NSSI. Yet, validation is still in progress and inclusion of NSSI to the DSM-5 has led to an ongoing discussion as some researchers argued that NSSI should be viewed as a disorder in its own right (In-Albon et al., 2013; Zetterqvist, 2015). Yet, others have stressed that NSSI should rather be considered an unspecific precursor for psychopathological development and suicidality and may therefore be of limited significance as a 'pure and sole' diagnostic entity (Ghinea et al., 2020). Moreover, the dichotomy of suicidal and non-suicidal behaviors has been criticized as artificial (Zetterqvist, Lundh, & Svedin, 2013) and it has been argued that self-harm and suicidality need to be viewed on a continuum as not to underestimate the risks involved with NSSI (Kapur et al., 2013). In essence, previous research depicted NSSI as complex phenomenon, which may possibly be viewed as a disorder in its own right. However,

[2] Here, it needs to be mentioned that diagnostic criteria for NSSI differ significantly from the formal of deliberate self-harm, which refers to self-injury, irrespective of suicidal or non-suicidal intention. Briefly, as NSSI is increasingly being studied, it could be characterized more precisely over the past decades.

and due to the elevated suicide risk associated with NSSI, a thorough understanding of potential causes and accompanying symptoms appears particularly important.

Table 2

Proposed Diagnostic Criteria for Nonsuicidal Self-Injury According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA, 2013)

A. In the last year, the individual has, on 5 or more days, engaged in intentional self-inflicted damage to the surface of his or her body of a sort likely to induce bleeding, bruising, or pain (e.g., cutting, burning, stabbing, hitting, excessive rubbing), with the expectation that the injury will lead to only minor or moderate physical harm (i.e., there is no suicidal intent).

Note: The absence of suicidal intent has either been stated by the individual or can be inferred by the individual's repeated engagement in a behavior that the individual knows, or has learned, is not likely to result in death.

B. The individual engages in the self-injurious behavior with one or more of the following expectations:

1. To obtain relief from a negative feeling or cognitive state.
2. To resolve an interpersonal difficulty.
3. To induce a positive feeling state.

Note: The desired relief or response is experienced during or shortly after the self-injury, and the individual may display patterns of behavior suggesting a dependence on repeatedly engaging in it.

C. The intentional self-injury is associated with at least one of the following:

1. Interpersonal difficulties or negative feelings or thoughts, such as depression, anxiety, tension, anger, generalized distress, or self-criticism, occurring in the period immediately prior to the self-injurious act.
2. Prior to engaging in the act, a period of preoccupation with the intended behavior that is difficult to control.
3. Thinking about self-injury that occurs frequently, even when it is not acted upon.

D. The behavior is not socially sanctioned (e.g., body piercing, tattooing, part of a religious or cultural ritual) and is not restricted to picking a scab or nail biting.

E. The behavior or its consequences cause clinically significant distress or interference in interpersonal, academic or other important areas of functioning.

F.	The behavior does not occur exclusively during psychotic episodes, delirium, substance intoxication, or substance withdrawal. In individuals with a neurodevelopmental disorder, the behavior is not part of a pattern of repetitive stereotypies. The behavior is not better explained by another mental disorder or medical condition (e.g., psychotic disorder, autism spectrum disorder, intellectual disability, Lesch-Nyhan syndrome, stereotypic movement disorder with self-injury, trichotillomania [hair-pulling disorder], excoriation [skin-picking] disorder).

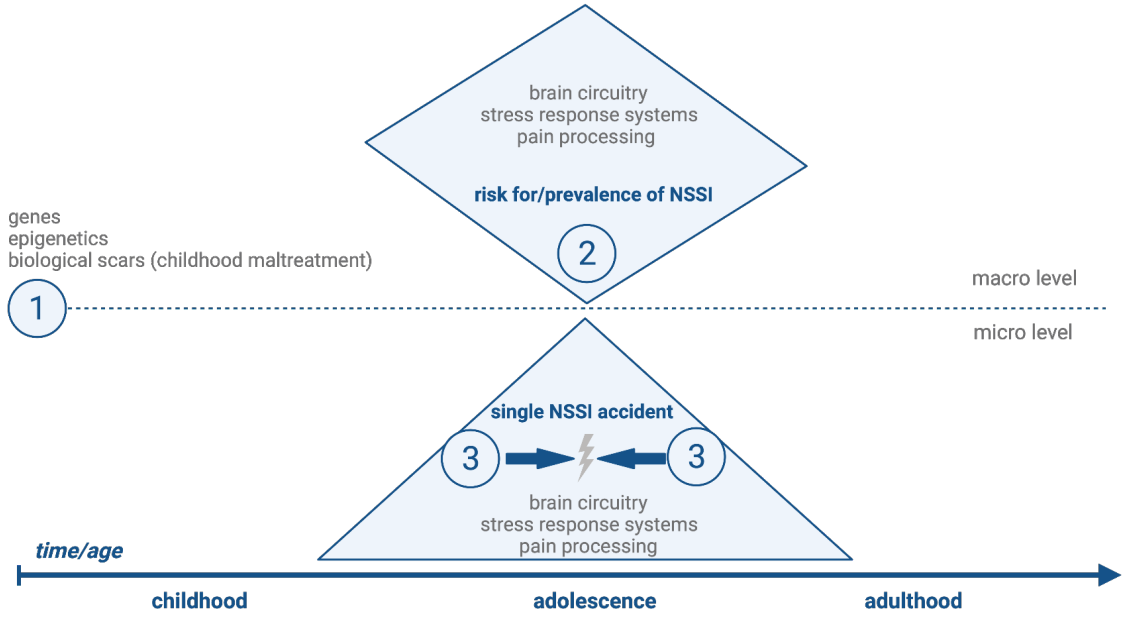
Epidemiological studies depict NSSI as a major concern in adolescence with current prevalence rates around 32% - 50% in hospitalized adolescents (Plener et al., 2010) and 19% in community samples (Muehlenkamp et al., 2012). Studies focusing on age-related community samples further suggest that between 13% - 45% of adolescents and around 4% of adults engage in NSSI at some point in their lifetime. However, rates are considerably higher among clinical samples of adolescents (40 - 60%) and adults (19% - 25%) (as reviewed in Nock, 2010). Besides, the general prevalence of NSSI in BPD patients is estimated between 65% - 80% (Brickman et al., 2014; Klonsky et al., 2003). Importantly, NSSI and suicide attempts lead to a tenfold increase of death by suicide in adolescence and can therefore be viewed as focal predictors in terms of suicide risk (Brent et al., 2013; Hawton & Harriss, 2007). And even though NSSI often ceases in late adolescence and early adulthood, the probability for risk-taking behaviors, suicidality and long-term mental health issues is significantly higher in individuals with a history of NSSI in adolescence (Brown & Plener, 2017). Briefly, NSSI is a rather common phenomenon in adolescence, which needs to be taken seriously due to the elevated suicide risk involved.

With regard to its multifactorial etiology, NSSI has recently been conceptualized by Kaess et al. (2021) based on a temporal framework. Here, the authors distinguish proximal traits (correlates), distal biological traits (predictors), and biological states accompanying NSSI. As shown in **Figure 2**, the authors suggest that mechanisms underlying NSSI can be distinguished on trait and state levels, whereby traits refer to relatively stable, enduring characteristics, patterns of behavior, or biological functioning. Traits are further conceptualized as the manifestation of altered behavioral and biological processes, which are not necessarily linked to NSSI. Thereby, traits are assumed to play an antecedent – and possibly causal – role in the pathophysiology of psychiatric disorders. Here, proximal traits refer to underlying and moderately stable biological processes, which are unlikely to change

within days or weeks. Examples encompass altered brain structures or endocrinological functioning. Distal traits encompass biological predispositions and vulnerabilities for NSSI, which either exist from birth and early childhood or develop over a long period of time. Here, examples encompass genetic factors and risk factors predicting the development of NSSI. In contrast, states refer to temporary ways of being, such as thinking or feeling, transient biological markers, and mechanisms reflecting the current disease status. States can be examined by investigating biological processes immediately before, during or after an NSSI episode. Since a comprehensive investigation of states and traits accompanying NSSI has potentially far-reaching consequences for the development and examination of therapeutic interventions, the current dissertation focusses on a more detailed examination of these factors.

Figure 2

Theoretical Model by Kaess et al. (2021) Contrasting (1) Distal Biological Traits (Predictors), (2) Proximal Biological Traits (Correlates), and (3) Biological States Directly Preceding or Following Nonsuicidal Self-Injury.



Note. Relevant risk factors and mechanisms for NSSI can be classified as trait or state factors as it is assumed that certain parameters, such as neurological or endocrinological mechanism involved, influence the expression of states and traits.

As mentioned above, NSSI likely has a multifactorial etiology, which is why findings on genetics, neurobiology, adverse childhood experiences and other relevant environmental and behavioral factors will be presented below. First, a recent review estimated the heritability of NSSI to be 40 - 60% and further concluded that interactions between certain genes and environmental stressors increase the likelihood for NSSI development (Kaess et al., 2021). With regard to epigenetics, research has additionally shown that the degree of methylation of the promoter region of the glucocorticoid receptor gene correlates positively with adverse childhood experiences and NSSI severity (Martín-Blanco et al. 2014), which suggests that adverse childhood experiences may increase the risk for NSSI development (Kaess et al., 2013; Serafini et al., 2017).

Empirical evidence further suggests altered frontolimbic networks in NSSI, which may be accompanied by emotion dysregulation, impulsivity, and reduced cognitive control (Phillips et al., 2003). However, research has not yet been able to prove reduced cognitive

control consistently (as reviewed by Kaess et al., 2021), which is why the common judgement of NSSI patients as being excessively impulsive needs further investigation. Besides, alterations of frontolimbic networks may also lead to reduced pain sensitivity during NSSI episodes (Kirtley, O'Carroll, & O'Connor, 2016). And despite the fact that the ecological validity of laboratory-based pain induction has been widely discussed, the finding of reduced pain sensitivity in NSSI patients has been replicated repeatedly. However, it has not yet been clarified whether reduced pain sensitivity results from previous self-harm or prospectively increases the risk to engage in self-harm (Kaess et al., 2021). With regard to endocrinological alterations, initial research characterized female adolescents with NSSI by attenuated cortisol responses to psychosocial stressors (Kaess et al., 2012), which may resemble blunted cortisol responses to NSSI. This finding has recently been replicated in an adolescent sample by comparing patients with NSSI and depression to healthy controls and patients with depression only (Klimes-Dougan et al, 2018). Here, frequency of NSSI moderated blunted cortisol responses as adolescents with multiple NSSI episodes exhibited lower cortisol levels than those with one or two lifetime episodes of NSSI. A recent study by our group further compared adolescents with NSSI to their siblings based on hair cortisol and salivary cortisol before and after sharing adverse childhood experiences as part of a diagnostic interview (Reichl et al., 2019). Here, NSSI patients could be characterized by higher levels of hair cortisol but decreased salivary cortisol during retrieval of adverse childhood experiences, while no such changes could be identified in the sibling group. Correspondingly, the authors suggested that altered HPA axis functioning may be traced back to adverse childhood experiences, which could act as a chronic stressor with the potential to attenuate the cortisol response. NSSI patients could further be characterized by decreased sensitivity to pain, which can possibly be traced back to a basal lack of endogenous opioids (Koenig et al., 2017). Hence, with regard to the biological foundations, genetic influences, neurological and endocrinological alterations seem to have an important effect on NSSI development and maintenance and may point to an etiological role of adverse childhood experiences.

Moreover, research indicated that demographic factors affect NSSI occurrence as NSSI is most common in early to mid-adolescence and often ceases in young adulthood (Zetterqvist et al., 2013). Besides, certain neurodevelopmental processes in adolescence seem to be related to increased risk-taking, impulsivity, and emotional reactivity, which, in turn, may increase the likelihood for NSSI (Casey et al., 2008). It has further been suggested that adverse childhood experiences such as parental neglect, abuse, or deprivation, increase the risk for

NSSI (Brown & Plener, 2017). Yet, the corresponding links are often inconclusive and may therefore be difficult to examine. For instance, sexual abuse may only be moderately related to NSSI development (Klonsky & Moyer, 2008) while parental critique, apathy (Tschan et al., 2015), and emotional abuse (Thomassin et al., 2016) have been associated with NSSI repeatedly. Similarly, direct forms of maltreatment, such as physical or sexual abuse, may not be associated with NSSI development, while indirect forms, such as witnessing domestic violence may be associated with self-injurious behavior (Maniglio, 2011). So taken together, it is still a matter of debate whether adverse childhood experiences constitute risk factors for NSSI development or whether they affect psychosocial functioning more generally and may thereby increase the risk for NSSI occurrence.

Demographic research further suggests gender differences as females engage in NSSI more often, especially when looking at clinical populations (Bresin & Schoenleber, 2015). Interestingly, NSSI methods also seem to differ by gender: while females most frequently engage in cutting, males rather engage in hitting against walls (Barrocas et al., 2012). With regard to social factors, dysfunctional relationships – and in particular bullying – seem to be key risk factors for NSSI development. Correspondingly, a large European study showed that NSSI patients have frequently been victimized in the past but further highlighted several protective factors, such as parent and peer support as well as prosocial behavior of the participants themselves (Brunstein Klomek et al., 2016). Moreover, NSSI seems to be more common within certain youth subcultures, such as 'gothic' or 'emo', than in the general population (Young et al., 2014) and a comprehensive review by Jarvi et al. (2013) showed that NSSI occurs more frequently after social contagion, which refers to friends or acquaintances engaging in NSSI. Notably, most included primary studies were published decades ago, which comes along with several methodological drawbacks, such as ambiguous inclusion criteria. Findings nonetheless suggest that initial NSSI engagement might be influenced by social contagion or by being exposed to NSSI through the media (Brown & Plener, 2017). Maintenance of NSSI has presumably more of an interpersonal function[3], which may reinforce over time. In summary, research suggests that development and maintenance of NSSI is influenced by several demographic and social factors encompassing age, female gender, history of adverse childhood experiences, victimization, and social contagion. Certainly, more research is needed to investigate these factors comprehensively.

[3] Such as receiving affection from others.

Comorbidities and Closely Related Disorders

Developmental psychopathology is often characterized by multiple and overlapping psychiatric diagnoses (Kamin & Kertes, 2017) and comorbidity seems to be particularly high in adolescents with BPD (Lenzenweger et al., 2007) and NSSI (Ghinea et al., 2020). For instance, BPD patients show significantly more externalizing and internalizing disorders and more frequent substance abuse compared to adolescent patients without BPD (Chanen et al., 2007; Ha et al., 2014; Kaess et al., 2013). It has further been estimated that up to 60% of BPD patients meet the diagnostic criteria for complex comorbidity, which has been defined as the interplay of externalizing and internalizing disorders (Eaton et al., 2011). Recently, it therefore has been suggested to treat complex comorbidity as a warning sign for potential BPD (Fonagy et al., 2015). Similarly, research indicates that NSSI patients often also meet the diagnostic criteria for affective disorders and PTSD (e.g., Ghinea et al., 2020; Koposov, Stickley, & Ruchkin, 2021) To shed more light on this distinction, three clinical pictures showing considerable symptomatic overlap with BPD and NSSI will be delineated in the following.

Affective disorders.

BPD and NSSI are often comorbid with affective disorders (Buelens et al., 2020), however, affective instability typically seen in BPD and NSSI can easily be confused with depressed mood characteristic for affective disorders (Sher et al., 2016). Similarly, differentiating BPD from bipolar disorder may be challenging due to symptomatic overlaps with affective lability, pronounced anger, impulsivity and suicidality (Ruggero et al., 2010). Yet, research suggests that clinical characteristics can be differentiated based on phenomenology and course of the disorder, comorbidity, treatment response, and family anamnesis (Bayes et al., 2014; Parker, 2014).

Posttraumatic stress disorder (PTSD).

Links between BPD, NSSI and adverse childhood experiences, which may have been experienced as traumatic events, have been widely studied due to overlaps in diagnostic criteria and phenomenological overlap between BPD and PTSD has even led to the hypothesis that BPD is a trauma-related disorder (Golier et al., 2003). Corresponding research indicated that exposure to violence in childhood or adolescence reinforces emotion dysregulation, which, in turn, resembles PTSD and BPD symptoms (Kuo et al., 2015). Another study examined baseline data from the *Collaborative Longitudinal Study of Personality Disorders* and compared female BPD patients to PTSD patients (Zlotnick et al.,

2003). Here, patients with BPD *and* PTSD showed elevated suicide proneness, impulsivity, higher general dysfunction and more frequent hospitalization, which not only suggests that diagnoses frequently co-occur but also that comorbidity of BPD and PTSD needs to be taken seriously. Moreover, BPD patients may experience victimization and traumatization when being impulsive or when engaging in unstable relationships, which may indirectly increase the risk of developing PTSD later on. Correspondingly, a literature review showed that between 30-70% of BPD patients receive an additional PTSD diagnosis while PTSD is only diagnosed in 3-6% of the general adult population (Frías & Palma, 2015). Similarly, PTSD and NSSI appear to be closely related since PTSD diagnoses at age 21 predict NSSI at age 26 in females (Nada-Raja & Skegg, 2011). Here, it has further been speculated that NSSI may be a means to cope with trauma symptoms and a corresponding systematic review by Smith et al. (2014) indicated that NSSI may offer an escape from intrusive thoughts, aversive emotional states, dissociation, and numbness, which is why the authors concluded that trauma symptoms may contribute to development and maintenance of NSSI. So taken together, BPD, NSSI and PTSD may act as mutual risk factors, yet future research needs to investigate if they share underlying etiopathogenic mechanisms.

Suicidal behavior disorder. As briefly mentioned above, current classification systems differentiate NSSI from suicidal acts by means of separate diagnostic criteria for NSSI and suicidal behavior disorder. Hence, and according to DSM-5 criteria (APA, 2013), NSSI is characterized by the absence of suicidal intent while suicidal behavior disorder clearly entails the intention to die from self-harm. In clinical practice, however, patients are oftentimes ambivalent about their underlying intention, which complicates an adequate distinction. As epidemiological studies demonstrate high comorbidities between NSSI and suicidal behavior disorder (e.g., Asarnow et al., 2011), it has been suggested to view suicidal intention on a continuum rather than as dichotomous categories (Brunner et al., 2014). Here, research on adolescent populations showed that 70% of NSSI patients attempted suicide at least once while more than 50% reported multiple suicide attempts (Nock et al., 2006). And, with regard to potential links between suicidality and NSSI in BPD patients, it has been estimated that about 75% attempt suicide at least once while around 10% may even die by suicide (Black et al., 2004). To sum up, although NSSI and suicidal behavior disorder have been differentiated formally, symptomatic overlap is rather the rule than the exception. For this reason, even

supposedly benign self-injurious acts should be taken seriously and likely requires treatment prior to chronification or attempted suicide.

Endocrinological Correlates of Psychopathology

General Endocrinological Principles

Research suggests altered stress responses in BPD and NSSI and it seems likely that altered endocrinological biomarkers mirror these stress responses, which is why some focal endocrinological principles will be explained below. The classic definition of endocrine tissue refers to a specialized ductless gland, which releases hormones into the bloodstream to act on a distant target (Bruyette, 2020). Generally speaking, hormones act directly on specific target cells, serve as releasers or inhibitors of other hormones, and transmit electrical impulses to neurons or as cotransmitters (so-called neuromodulators). They further regulate various biological processes, such as mobilization, storage and distribution of nutrients (Marketon & Glaser, 2008). Hormones further act directly on specific target cells, serve as releasers or inhibitors of other hormones, and transmit electrical impulses to neurons or as cotransmitters (so-called neuromodulators). In addition, most hormones exert their actions by binding to specific protein structures of target cells called receptors. Hormones are further classified according to their structure[4], their site of synthesis[5], and according to their function. The latter refers to a variety of processes, such as growth, maturation, sleep, pain, feeding, reproduction, metabolism, affective states, and even personality traits. Information processing of the endocrine system is roughly comparable to the nervous system and thus crucial for the organism. Lastly, the endocrine system carries out internal checks by utilizing some form of negative feedback control to maintain homeostasis (see below).

Moreover, the endocrine system can be divided into four subsystems, respectively the HPA axis, the hypothalamic-pituitary-thyroid (HPT) axis, the hypothalamic-pituitary-gonadal axis and the hypothalamic-neurohypophyseal system. These subsystems are regulated by distinct endocrine glands, which produce and secrete hormones of different chemical structures, such as peptides, steroids and neuroamines. Classic endocrine glands encompass pituitary, hypothalamus and adrenal glands. Hormones can further be distinguished depending on the site of action: as paracrine hormones affect cells close to the source of the paracrine hormone, autocrine hormones operate in the cell releasing these

[4] Polypeptides, glycoproteins, amino acid derivatives, and steroid hormones can be distinguished.
[5] Here, neurohormones are produced based on neural tissue. Glandular hormones are produced through endocrine glands. Paracrine signaling refers to hormones produced in the respective target tissues.

hormones, and (3) endocrine hormones travel to their targets after release into the bloodstream.

Endocrinological Correlates of Stress

Stress refers to a state, where the individual perceives a real or anticipated challenge to homeostasis, which requires some sort of adaptive response (Wolf, 2008). Correspondingly, a stressor has been defined as a specific event inducing stress and can be physical (e.g., thirst, pain) or psychological (e.g., worry, fear) in nature. Stressors can furthermore be acute (e.g., an upcoming exam) or chronic (e.g., constant work overload). And, as individuals perceive stressors differently, the individual impact can be determined by evaluating subjective stressor appraisal and available coping resources (Lazarus, 1993). Put differently, responding to a stressor involves several actions by multiple stress-responsive systems, which interact in a highly coordinated manner. Stressors are processed by different neuroendocrine structures, which involve interactions between nervous and endocrine systems (Netter, 2015). For instance, the so-called fight-or-flight response occurs when the amygdala reacts to a threat, whereupon the hypothalamus activates the sympathetic nervous system so that adrenaline can be released. This response involves several physical alterations such as increases in heart rate, breathing frequency and sweat production as well as the perception of 'feeling stressed'. A slower response is initiated by the HPA axis when glucocorticoids pass the blood-brain-barrier.

Besides, certain endocrinological systems adapt to changing conditions by employing internal thresholds while others aim for maintaining steady levels of metabolites or electrolytes. For instance, hormones of the HPA axis are governed by homeostasis, which has initially been defined as coordinated physiological process to maintain most of the steady states in the organism including reciprocal neuroendocrine actions, hence feedforward and feedback mechanisms (Cannon, 1939). Within feedback loops, target cells respond to endocrine stimulation, which lessens stimulation of endocrine systems and restores internal conditions towards normal (see **Figure 3**). Aside from that, hormones are released rhythmically and according to ultradian, circadian, or lunar cycles (Kalafatakis, Russell, & Lightman, 2019). Ultradian cycles are defined as several endocrinological changes per day and for instance apply to insulin, which is produced by beta cells of pancreatic islets. Circadian cycles are defined as endocrinological alterations within 24-hour periods and for instance apply to melatonin, which is released by the pineal gland at night to control the sleep-wake

cycle. Lunar cycles can be observed in gonadal hormones such as estradiol and luteinizing hormone, which drop in the menstrual phase, rise in the follicular phase, and peak at ovulation. Yet, hormones may also fluctuate between seasons or over the course of development and cyclical malfunctions may point to various disorders such as depression or infertility. Malfunctioning with regard to amplitude of hormone production, hence so-called neuroendocrine hyper- or hypoactivity, may indicate specific endocrinological diseases. In short, neuroendocrine effects on brain and body as well as interactions with several neurotransmitter systems mirror stress regulation capacities and thereby potential relationships with psychopathology (Kamin & Kertes, 2017).

The hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is regulated by glucocorticoids acting on different intracellular receptors, namely type I/mineralocorticoid receptors and type II/glucocorticoid receptors, which differ in terms of distribution and affinity. Glucocorticoids are critical for energy mobilization and distribution to multiple organ systems to assure energy availability (Herman, 2013) and glucocorticoids further influence multiple neurotransmitter systems, such as the cholinergic, noradrenergic, serotonergic and dopaminergic systems (Elsenbruch & Wolf, 2015). With regard to HPA axis functioning, corticotropin-releasing hormone (CRH) is typically released by the hypothalamus according to a circadian rhythm. This stimulates ACTH production in the anterior pituitary, whereupon cortisol production is prompted in the adrenal cortex. As shown in **Figure 3A**, the HPA axis modulates its activity based on feedforward and feedback mechanisms, whereby negative feedback mechanisms primarily affect pituitary, hypothalamus, and hippocampus (Morris et al., 2012; Wingenfeld et al., 2010). Briefly, the HPA axis dynamically adapts to changing environmental demands by maintaining an optimal homeostatic state.

However, HPA axis is not only responsible for maintaining homeostasis under normal conditions but also for regulating stress responses (Lightman, 2008), whereupon CRH secretion increases rapidly. Here, stress regulation is assumed to have differential effects depending on the duration of cortisol exposure. Acute and transient cortisol reactivity are considered adaptive, while long-term, dysregulated cortisol secretion – for instance due to chronic stress – is considered maladaptive (Stalder et al., 2017). Acute cortisol reactivity is reflected by a spike of peripheral cortisol levels in response to a stressor, which can be measured in saliva approximately 20 minutes after stressor onset (Dickerson & Kemeny, 2004). Following stressor removal cortisol decreases rapidly to baseline (Tackett et al., 2013).

Correspondingly, the endocrine stress response can be measured using peak cortisol levels after stressor exposure relative to pre-exposure levels (*reactivity*) or by calculating the rate of decrease in cortisol levels following stressor removal (*recovery*). In contrast to acute cortisol reactivity, long-term cortisol exposure has been associated with a various mental health issues and physical changes, such as depression, PTSD, and hippocampal damage (Cranston, 2014; Malisiova et al., 2021). Research has further shown that cortisol levels change systematically over the lifespan, whereby pre- and postnatal development seems to be particularly sensitive to stress (Lupien et al., 2005). In fact, the HPA axis is highly reactive after birth, becomes hyporesponsive during childhood and approaches adult-like functioning from puberty on. Thereby, adolescents no longer show cortisol hyporesponsivity typical for childhood, but rather adultlike responses to acute stressors (Tackett et al., 2013). Yet, it has also been suggested that the HPA axis can be 'reprogrammed' based on individual experiences of emotional stress (Quevedo et al., 2012) and empirical evidence suggests that adverse childhood experience lead to a shift in HPA axis functioning from elevated cortisol levels in childhood to blunted cortisol levels in adulthood (Trickett et al., 2010). Besides, links between pituitary volume and adverse childhood experiences are assumed to lead to HPA axis attenuation over the course of development (Kaess et al., 2018). Taken together, the HPA axis can be considered a crucial endocrine system, which processes acute and chronic stressors and which is shaped base on an individual's trajectory. However, a stronger focus on developmental alterations is needed to examine characteristic endocrine profiles in BPD and NSSI patients in detail.

The hypothalamic-pituitary-thyroid (HPT) axis. Another stress-responsive endocrine system is the HPT axis, which is responsible for synthesis and production of thyroid hormones (Gao et al., 2019). Thyroid hormones regulate various metabolic functions, such as carbohydrate and fat metabolism, protein synthesis, neural development, osseous growth, cardiovascular and renal functioning. With regard to functioning of the HPT axis, neurons in the hypothalamic paraventricular nucleus synthesize the tripeptide thyrotropin-releasing hormone (TRH), which is delivered to the anterior pituitary to prompt synthesis and release of thyroid-stimulating hormone (TSH). TSH then binds to receptors on the surface of thyroid follicle cells, which stimulates adenylate cyclase (Zoeller et al., 2007). Eventually, this stimulates production of iodothyronines, i.e. the prohormone thyroxine (T4) and a smaller fraction of the biologically active hormone triiodothyronine (T3). These thyroid hormones are

carried to various target tissues by specific proteins. Total T4 and T3 levels not only reflect changes in thyroid function, but are also highly variable indicators of thyroid function as they vary depending on the amount of serum binding proteins. Serum free hormone measurements (i.e. T4 or T3 unbound to serum proteins; fT4 and fT3) are not affected by alterations in binding proteins and can therefore be considered more reliable measures of thyroid function. Approximately 0.3% of T3 and 0.02% of T4 are available in the periphery (in free), hence in their biologically active form (Russell et al., 2008). Hence, as concentrations of free T4 and T3 are extremely low, sufficient volumes of serum must be collected. Importantly, and as shown in **Figure 3B**, T4 and T3 exert negative feedback to regulate pituitary TSH release and activity of hypothalamic TRH neurons (Zoeller et al., 2007). As circulating T4 and T3 levels fluctuate markedly, TSH is considered a suitable diagnostic marker of thyroid functioning. TSH is regulated by negative feedback of the HPT axis and TRH from the hypothalamus. TRH release, in turn, is regulated by thyroid hormones and neural inputs relaying information on various bodily states such as food availability, body temperature and cardiovascular functioning (Zoeller et al., 2007). However, the thyroid gland is not only controlled by TSH activity but also by its interactions with iodine availability. Eventually, thyroid hormones are cleared from the liver following sulfation or sulfonation by sulfotransferases and following glucuronidation by UDP-glucoronosyl transferase, whereupon modified thyroid hormones are eliminated through the bile. For a more in-depth overview, the comprehensive review by Zoeller et al. (2007) is recommended.

Associations between thyroid activity and mental disorders have been studied for over a century (Hennessey & Jackson, 1996) and a special interest applies to affective disorders (Sullivan et al., 1997). Yet, most corresponding research has been carried out in the early 1970s and does therefore not necessarily correspond to contemporary empirical standards. Back then, TRH became available for clinical testing, whereupon the so-called TRH stimulation test had been developed[6]. Early studies point to blunted TSH in depressed patients, yet the underlying mechanism has been discussed controversially. Hence, it has been suggested that glucocorticoids, which are frequently elevated in depression may inhibit HPT axis functioning (Dwyer et al., 2020). However, as TSH levels frequently stabilize after recovery from depression while cortisol presumably does not (Bockting et al., 2012), research

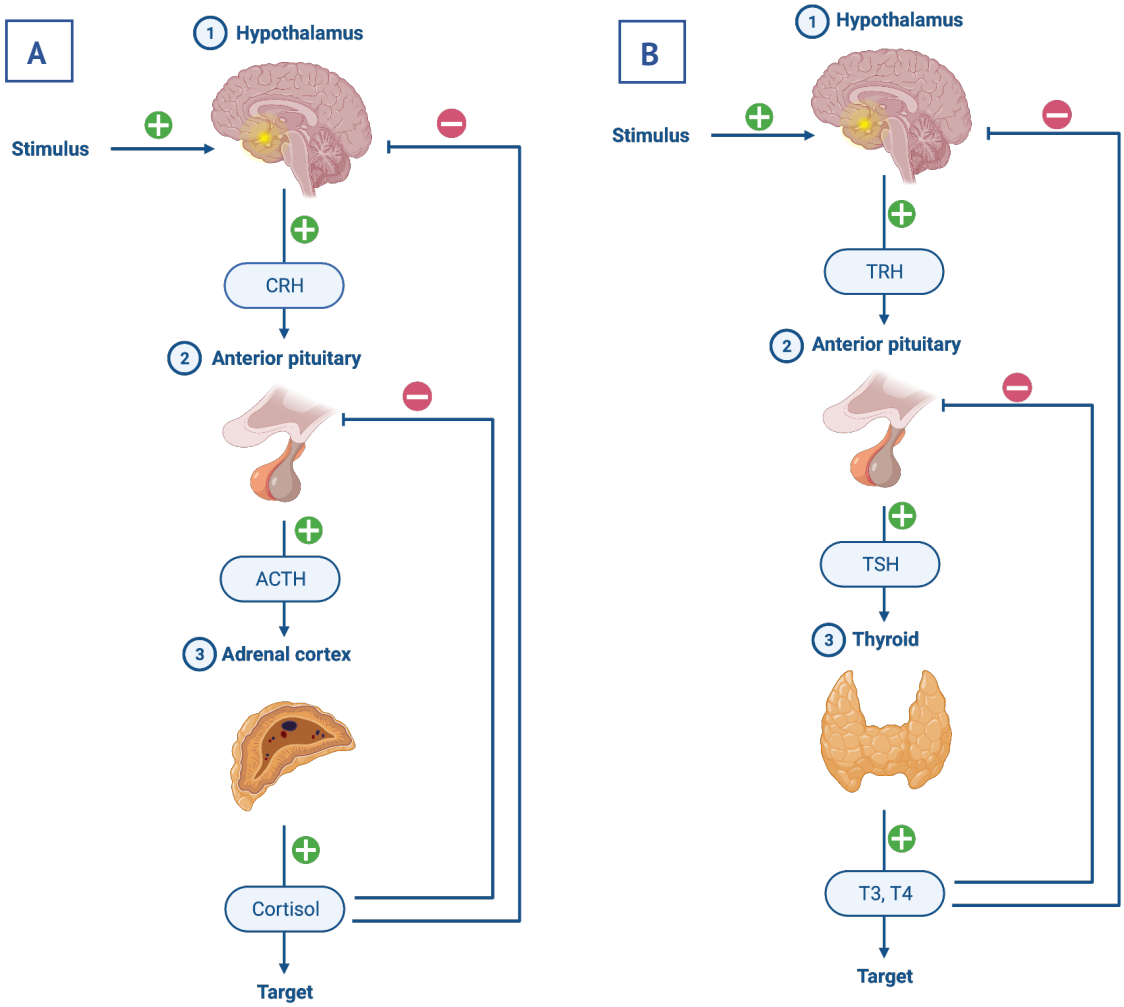
[6] For the TRH stimulation test, TRH is administered intravenously and TSH levels are measured multiple times by taking blood samples taken from a peripheral vein. The TRH stimulation test had been evaluated in somatic and psychiatric disorders and can for instance be used to diagnose hypothyroidism.

suggests that TSH and cortisol secretion are not necessarily linked. Blunted TSH may therefore be viewed as a diagnostic state marker (Mokrani et al., 2020). Further, research suggests that hypothyroidism frequently accompanies affective disorders and preliminary evidence implicates subclinical hypothyroidism as a risk factor for major depression and concomitant of treatment-refractory depression (Loh et al., 2019). Nonetheless, and due to the high variability associated with HPT axis measurements, findings on thyroid functioning in mental disorders need to be interpreted with caution. This seems particularly important as there is a close relationship between thyroid dysfunction, age, and medication use, so that corresponding studies must be designed and evaluated carefully.

Interconnections between the HPA and HPT axes. As both the HPA and the HPT axes originate in the hypothalamus, they display several interconnections and likely affect each other (Min et al., 2012). In addition, previous work by Helmreich et al. (2005) demonstrates that both acute and repeated stressors affect hormone secretion of these endocrine axes. Besides, evidence suggests associations between glucocorticoids and TSH secretion (Mokrani et al., 2020). However, it has not been clarified yet whether the site of action is the hypothalamus, pituitary or both (Duval et al., 2006). Research on rodents further demonstrated that glucocorticoids inhibit peripheral conversion of T4 to T3, which may lead to stress-induced decreases of serum T3 levels (Bianco et al., 1987). However, it is unclear whether findings based on animal models can be applied to human endocrine functioning. Taken together, both the HPA and the HPT axes are highly responsive to stress, which is why potential cross-regulation and communication between these endocrine axes seems worth investigating. Investigating corresponding investigations using adolescent samples may further underpin the biological basis for BPD and NSSI development as this developmental period is marked by heightened stress reactivity (Simmons et al., 2015).

Figure 3

(3A) *Schematic Illustration of the Hypothalamic-Pituitary-Adrenal (HPA) Axis.* **(3B)** *Schematic Illustration of the Hypothalamic-Pituitary-Thyroid (HPT) Axis.*



Note. **(3A)** With regard to HPA axis functioning, the three endocrine glands, i.e., hypothalamus, pituitary gland, and adrenal cortex, are regulated by neuroendocrine feedback interactions. Thereby, the HPA axis regulates stress responses and maintains homeostasis. CRH = corticotropin-releasing hormone; ACTH = adrenocorticotropic hormone. **(3B)** With regard to HPT axis functioning, the three endocrine glands, i.e., hypothalamus, pituitary gland, and thyroid gland, are regulated by neuroendocrine feedback interactions to maintain homeostasis. TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine.

Research Questions and Methodology of the Current Dissertation

As reviewed in the previous sections, existing research indicates links between endocrinological functioning and stress sensitivity in BPD and NSSI, yet developmental influences have been investigated insufficiently so far. Therefore, the current dissertation aimed at examining associations between endocrinological markers and BPD and NSSI with special consideration of development in adolescence. To evaluate focal hypotheses of the biosocial theory for BPD (Linehan, 1993; Crowell et al., 2009) and the temporal framework for NSSI (Kaess et al,. 2021), three different studies were conducted by building on separate research designs. In **Study 1**, we aimed at providing a general overview of HPA axis functioning in BPD patients by investigating endocrine alterations and examining contributing factors based on a meta-analytic design. In **Study 2**, we examined the interplay between HPA axis functioning and psychopathology in BPD patients of different ages compared to healthy controls based on a cross-sectional design. Developmental alterations were examined based on the cortisol awakening response (CAR), which is a particularly sensitive assessment of cortisol production over a limited period of time. Given that states of heightened stress typically precede acts of NSSI and given that NSSI can be considered an important precursor of BPD development, **Study 3** was conducted. Here, we primarily aimed at evaluating interconnections between HPA and HPT axis markers in adolescents presenting with NSSI and a variable number of BPD symptoms based on a cross-sectional design. The corresponding endocrinological markers were correlated with focal psychopathological characteristics to take a dimensional perspective on stress, biological foundations, and development in BPD and NSSI patients.

First Manuscript: The Hypothalamic-Pituitary-Adrenal Axis

Drews, E., Fertuck, E. A., Koenig, J., Kaess, M., & Arntz, A. (2019). Hypothalamic-Pituitary-Adrenal Axis Functioning in Borderline Personality Disorder: A Meta-Analysis. *Neuroscience & Biobehavioral Reviews*, *96*, 316-334. https://doi.org/10.1016/j.neubiorev.2018.11.008

As described above, prior research assumed abnormal stress responsivity in BPD patients, which has for example been illustrated by Kuhlmann and colleagues (2013), who characterized BPD patients by *'increased stress vulnerability, disturbed HPA axis functioning and alterations in the size and activation of structures involved in central stress regulation'* (p. 130). Also, prior studies linked 'acute' BPD symptoms, such as impulsivity and emotion dysregulation, to poor stress resistance (Wingenfeld et al., 2010; Zimmerman & Choi-Kain, 2009) and blunted cortisol responses to chronic stress, assumedly due to a downregulation of the HPA axis. Yet, as disorder-specific cortisol reactivity has been investigated sparsely and as the role of comorbid disorders has been investigated insufficiently, the following three questions were posed in **Study 1**: first, do BPD patients show a specific endocrinological profile based on HPA axis activity? And if so, what role does the type of HPA axis measurement play? Second, how are HPA axis markers related to stress responsivity? And third, do covariates, such as age and gender, affect HPA axis measurements in BPD patients? Based on prior qualitative reviews (Wingenfeld et al., 2010; Zimmerman & Choi-Kain, 2009), we hypothesized that BPD patients would show altered stress responsivity and a correspondingly altered endocrinological profile.

The meta-analysis was preregistered using a web-based protocol on the *International Prospective Register of Systematic Reviews* by the Centre for Reviews and Dissemination (PROSPERO; registration number CRD42017062312) and PRISMA statement guidelines were applied (Liberati et al., 2009; Moher et al., 2015). Predefined search and eligibility criteria were used to guide inclusion of primary studies. The eligibility assessment was performed by five reviewers in a standardized manner. Primary studies were included if all inclusion criteria were reported in the respective publications or if corresponding authors provided missing details. Data collection took place using a digital data extraction sheet based on recommendations by Tacconelli (2010). Extractions were completed in duplicate and information was extracted on general information about the study, study and participant characteristics, study design, results, and details necessary for the risk of bias assessment.

Statistical analyses were based on random effect models and Hedges' *g* to account for small sample sizes. Heterogeneity was measured using chi-square *Q*-statistics and I^2-Indices. Meta-regressions were calculated for potential covariates given that at least ten publications within one meta-analytic comparison reported on the potential covariate. Publication bias was examined based on funnel plots, Egger's test and Duval and Tweedie's trim and fill procedure.

The search resulted in 804 publications, of which 37 studies (*k* = 81, BPD *n* = 803, controls *n* = 1092) were considered suitable for meta-analytic comparisons. Due to methodological differences, results were grouped around for prevailing experimental paradigms, namely singular (*k* = 43) and continuous cortisol assessments (*k* = 5), pharmacological challenge tests (*k* = 8), and psychosocial challenges (*k* = 13). Thirty-four publications compared BPD patients (*n* = 758) to healthy controls (*n* = 902), seven studies compared BPD patients (*n* = 105) to patients with depression (*n* = 113), and four studies compared BPD patients (*n* = 72) to patients with other personality disorders (*n* = 77). Most publications reported on measures based on saliva (*k* = 14), plasma (*k* = 13), or serum (*k* = 8). With regard to endocrinological profiles, differences between BPD patients and healthy controls became apparent as BPD patients showed elevated continuous cortisol and blunted cortisol following psychosocial challenges. No group differences could be discerned for assessments on singular cortisol or cortisol after pharmacological challenges. Meta-regressions demonstrated potential covariates for singular cortisol assessments, such as the number of matched participant characteristics, and for psychosocial challenges, such as study quality. Publication bias was evident for some meta-analytic comparisons.

In accordance with the biosocial theory, findings reported in **Study 1** suggest a specific endocrinological profile in BPD patients as cortisol assessments applying psychosocial challenges and continuous cortisol measures yielded significant group differences. The finding of blunted cortisol responses to psychosocial challenges supports the hypothesis that hypoactivity of the HPA axis has initially been caused by an overactive HPA axis. However, as only a minority of studies assessed or reported childhood trauma, this assumption could not be tested directly. Elevated continuous cortisol in BPD patients furthermore pointed to elevated inner tension and more frequent daily hassles. Correspondingly, findings suggest that assessments based on continuous cortisol measures may be considered particularly reliable measurements of basal HPA axis activity. Based on the meta-analytic approach, it could further be shown that certain study characteristics affected potential group differences and should therefore be monitored closely in future studies. Taken together, **Study 1** can be

characterized by its methodological rigor and multiple included meta-analytic comparisons. With regard to potential limitations, however, most primary studies did not report on subjective stress experiences, which is why associations between stress perception and HPA axis activity could not be operationalized. Nonetheless, and given that cortisol can be considered a relatively unbiased and dynamic marker of stress responsivity, **Study 1** laid an important foundation for the current state of research on HPA axis functioning in BPD patients.

Second Manuscript: The Hypothalamic-Pituitary-Adrenal Axis and Development

Rausch, J., **Flach, E.**, Panizza, A., Brunner, R., Herpertz, S. C., Kaess, M., & Bertsch, K. (2021). Associations Between Age and Cortisol Awakening Response in Patients with Borderline Personality Disorder. *Journal of Neural Transmission, 128*(9), 1425-1432. https://doi.org/10.1007/s00702-021-02402-3

Evidence suggests that BPD patients display altered stress responsivity and **Study 1** indicates that abnormal HPA axis functioning mirrors such alterations adequately. As prior research suggested that maladaptive neuroendocrine processes can reliably be examined using the CAR and its trait measures 'area under the curve with respect to the ground' (AUC_G) and 'mean cortisol increase' (MnInc; Pruessner et al., 2003), **Study 2** was designed. Here, empirical findings indicate less attenuated, respectively increased CARs in BPD patients (Lieb et al., 2004; Rausch et al., 2015). Yet, the impact of developmental alterations has been studied insufficiently so far. Therefore, it seems debatable whether BPD chronicity influences the CAR and whether CAR patterns are stable over the life course, given that BPD traits usually peak in early adulthood and often decline afterwards (Kaess et al., 2014). **Study 2** therefore focused on developmental differences in BPD patients of different ages as measured with the CAR. Based on the findings reported in **Study 1**, we expected CARs in female BPD patients to be increased compared to those of healthy controls (HC). On the assumption that the CAR is a correlate of BPD chronicity, we further expected older BPD patients to show higher CARs than younger ones.

Age-specific effects of HPA axis functioning were examined by comparing BPD patients between 15 - 40 years to age-, sex- and intelligence-matched HC based on a cross-sectional design. Clinical assessments comprised disorder-specific questionnaires and interviews, such as the *International Personality Disorder Examination* (IPDE; Loranger et al., 1994), the *Borderline Symptom List* (BSL-23; Bohus et al., 2009) and the *Childhood Trauma Questionnaire* (CTQ; Bernstein et al., 1994). CARs were assessed on two consecutive weekdays using salivette devices at awakening and 30, 45, and 60 min later. With regard to statistical analyses, group differences and age effects in cortisol data were examined using mixed-design analyses of covariance (ANCOVA) with the between-subject factor group (BPD vs. HC), the within-subject factor time after awakening (0, +30, +45, +60), and the continuous predictor age. ANCOVAs were repeated with potential confounders as control factors and additional

ANCOVAs were calculated to examine AUC_G and MnInc. Dunn's multiple comparisons including Bonferroni corrections were used post hoc to examine significant effects of time or group by time. Pearson's correlations were used for analyses examining associations with age.

Across participants, CARs showed an inverted U-shape, yet levels tended to be higher in BPD patients across most time points. The corresponding repeated-measures ANCOVA demonstrated a significant main effect of time point and significant interactions between group × age, respectively group × age × time point, which suggests differential associations between age and CAR in BPD patients exclusively. Moreover, positive correlations between age and CAR were present in BPD patients but not in healthy controls. Findings for age and AUC_G, respectively MnInc, pointed in a similar direction. Effects remained stable after controlling for medication use, contraceptive use, smoking, comorbid depression or PTSD diagnoses, and childhood trauma. Thereby, findings not only demonstrate increased CARs in BPD patients but further suggest that endocrine alterations in BPD patients increase with age.

Findings from **Study 2** further strengthen assumptions of the biosocial theory that BPD emerges in a developmental context and designate elevations of the CAR as an important correlate of BPD chronicity. Positive correlations between HPA axis dysfunction and duration of BPD symptoms further indicate that stress vulnerability plays a crucial role for BPD development. Thereby, **Study 2** illustrates that development-related approaches are particularly important to gain a thorough understanding of HPA axis functioning and altered stress responsivity in BPD patients. However, as age was examined cross-sectionally, longitudinal research is needed to examine potential associations between HPA axis functioning and physical health in BPD patients in more detail. Besides, and as only parts of the sample were adolescent, larger corresponding samples of different ages are needed to investigate HPA axis functioning in BPD patients prior to chronification. **Study 3** aimed to fill this gap by examining endocrine markers of the HPA and the HPT axes in a fully adolescent sample.

Third Manuscript: The Hypothalamic-Pituitary-Thyroid Axis

Flach, E., Koenig, J., van der Venne, P., Parzer, P., Resch, F., & Kaess, M. (2021). Hypothalamic-Pituitary-Thyroid Axis Function in Female Adolescent Nonsuicidal Self-Injury and its Association with Comorbid Borderline Personality Disorder and Depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 111,* 110345. https://doi.org/10.1016/j.pnpbp.2021.110345

Findings from **Study 1** and **Study 2** reflect a growing interest in endocrinological markers for examining stress responsivity in patients with BPD and NSSI. Yet, next to HPA axis markers, HPT axis markers may mirror biological mechanisms underlying stress responsivity. **Study 3** therefore aimed at investigating the corresponding endocrinological profiles in adolescent NSSI patients and associations between HPT axis markers, cortisol, and dimensional psychopathological characteristics, such as adverse childhood experiences. Based on earlier findings, we hypothesized that NSSI patients would show altered HPT axis functioning, i.e. elevated thyroid-stimulating hormone (TSH), decreased free triiodothyronine (fT3), free thyroxine (fT4) and a decreased ratio of these hormones (fT3/fT4 ratio). Psychopathological characteristics, such as symptomatic distress, were expected to be associated with stronger blunting of HPT axis hormones and cortisol.

Data for the present set of analyses were collected from a consecutive help-seeking sample presenting at the outpatient clinic for risk-taking and self-harm (AtR!Sk; Ambulanz für Risikoverhalten und Selbstschädigung) at the Department of Child and Adolescent Psychiatry, University Hospital Heidelberg[7]. Thyroid levels and cortisol were investigated in adolescent NSSI patients showing a variable number of BPD criteria. NSSI patients (n = 116) were compared to healthy female adolescents (n = 41) and HPT axis hormones and cortisol were investigated based on serum-based blood draws taken around 0900h by qualified medical staff in a standardized manner. Psychological instruments included interviews and

[7] The specialized outpatient clinic has been launched in 2013 since respective health-care services are usually characterized by long waiting and high expenses through frequent inpatient stays. AtR!Sk primarily aims at averting chronification and long-term deterioration of symptoms. In AtR!Sk, risk-taking and self-harm behaviors are treated, which includes NSSI, suicide attempts, binge-drinking and substance abuse, as well as excessive media and internet use, sexual risk-taking and impulsive and delinquent behavior (Hessels et al., 2018). The treatment concept of AtR!Sk is characterized by low-threshold initial contacts, comprehensive diagnostics and tailored therapy for adolescents presenting with risk-taking and self-harm behavior.

questionnaires, such as the *Self-Injurious Thoughts and Behaviours Interview* (SITBI-G; Fischer et al. 2014), the *Depression Inventory for Children and Adolescents* (DIKJ, Stiensmeier-Pelster et al., 2000), the *Childhood Experience of Care and Abuse Questionnaire* (CECA.Q Smith et al., 2002), and the *Symptom-Checklist-90-Revised* (SCL-90-R; Derogatis & Savitz, 1999). Group differences on endocrinological parameters were analyzed using regression analyses. Associations between hormonal and clinical characteristics were analyzed using Pearson's correlations and semipartial correlations. Due to significant group differences with regard to smoking status, this variable was included as covariate for the subsequent statistical analyses.

With regard to demographic details, approximately one third of the NSSI group (n = 34, 29%) met sufficient criteria for a BPD diagnosis based on the clinical interview. Besides, nearly two third of the NSSI group (n = 72, 62%) met the diagnostic criteria for depression. NSSI patients reported a significant higher frequency of adverse childhood experiences compared to HC. With regard to endocrinological parameters, NSSI patients showed significantly lower fT3/fT4 ratios than HC. Furthermore, negative correlations were present between BPD severity and TSH, fT3, fT3/fT4 ratio and smoking status. Depression severity correlated negatively with fT3, fT3/fT4 ratio and smoking status. Symptomatic distress correlated negatively with TSH, fT3 and fT3/fT4 ratio. Group differences for singular cortisol measures failed to reach statistical significance, which corresponds to findings from **Study 1**.

Taken together, findings from **Study 3** provide evidence that endocrinological alterations in NSSI and BPD are present at an early developmental stage, which supports central assumptions of the biosocial theory stating that reciprocal reinforcing transactions between biological vulnerabilities and environmental risk processes potentiate emotion dysregulation as well as the emergence of identifiable features and maladaptive coping strategies in mid- to late adolescence, which indicate a heightened risk for later BPD. Moreover, results indicate altered fT3/fT4 as a biological correlate of NSSI in adolescence. Initially, however, altered fT3/fT4 may be traced back to disrupted conversion from T4 to T3, which has previously been associated with fatigue, depression and concentration difficulties (Medici et al., 2015). Yet, as endocrinological markers were not only related to disorder-specific measures but also to general psychopathology, dysfunction of the HPT axis may also represent a non-specific mechanism promoting NSSI via general psychopathological distress. In accordance with the temporal framework by Kaess et al. (2021), **Study 3** suggests that HPT axis dysfunction constitutes a proximal biological trait, hence an underlying biological alteration observed among individuals engaging in NSSI. Nonetheless, since analyses were

based on singular endocrinological measures, long-term and dynamic endocrinological assessments are needed to confirm the diagnostic value of HPT axis markers for BPD and NSSI in future research.

Discussion

The current dissertation examined associations between endocrinological and psychopathological characteristics in patients with BPD and NSSI based on the biosocial theory for BPD (Linehan, 1993) and a recently proposed temporal framework for NSSI (Kaess et al., 2021). For this purpose, three separate studies were carried out. First, **Study 1** used a meta-analytic design to quantify the current state of research on HPA axis functioning in BPD patients, whereby BPD patients could be characterized by blunted cortisol responses to psychosocial challenges and elevated continuous cortisol. As proposed by the biosocial theory, these endocrine patterns presumably mirror altered stress regulation capacities and may confirm a HPA axis burnout phenomenon as described by Danese and McEwen (2012). However, as high-risk transactions with caregivers proposed by the biosocial theory were not investigated, the corresponding hypotheses could not be evaluated. Put differently, **Study 1** did not evaluate whether altered HPA axis functioning as a biological vulnerability leads to high-risk transactions with caregivers or if high-risk transactions with caregivers lead to altered HPA axis functioning as a biological vulnerability. Nonetheless, especially the finding of altered endocrinological functioning due to psychosocial challenges suggests that interpersonal encounters with close ones, such as caregivers, play a decisive role in this potentially vicious cycle. Findings from **Study 1** further match the earlier findings on stress exposure and HPA axis functioning in BPD (Bourvis et al., 2017; Wingenfeld et al., 2010; Zimmerman & Choi-Kain, 2009), yet it needs to be emphasized that most primary studies included in **Study 1** did not operationalize stress exposure. In addition, diverging definitions of stress regulation may complicate a thorough evaluation of the corresponding theoretical background. Future research therefore needs to examine links between stress exposure and HPA axis functioning more directly.

Moreover, and due to the observation that development inherently affects endocrinological functioning, **Study 2** was conceptualized. Here, the cortisol awakening response (CAR) was examined in female BPD patients and healthy controls with special consideration of age. CARs were assessed on two consecutive weekdays to examine basal HPA axis activity and findings entailed increased CARs in BPD patients, which may confirm links between early life stress and HPA axis attenuation in this patient group. As CARs were elevated with increasing age in BPD patients, the hypothesis on mutual effects of biological vulnerabilities and high-risk transactions with caregivers by the biosocial model could

indirectly be supported. Hence, elevated CARs with increasing age suggest that histories of high-risk transactions manifests through aberrant HPA axis functioning, which is why a developmental perspective on endocrine markers may be particularly revealing.

Based on the assumption that a developmental perspective allows for examining the specificity of endocrinological markers, **Study 3** was implemented. Here, adolescents with NSSI and showing a variable number of BPD symptoms were compared to healthy adolescents based on several HPT axis markers and cortisol. Results showed blunted fT3/fT4 ratio values in NSSI patients, which may be regarded as biological correlate of NSSI in adolescence. Furthermore, negative correlations between several endocrinological markers and psychopathological characteristics were found, i.e. fT3, fT3/fT4 ratio, TSH and severity of BPD symptoms, depression scores and symptomatic distress. Cortisol was not significantly altered in adolescents with NSSI, however, this can possibly be attributed to the fact that singular cortisol measurements were taken while repeated measurements would have been required. With regard to the temporal framework, HPT axis dysfunction may presumably be considered a proximal biological trait, hence an underlying and moderately stable biological processes, which is closely related to NSSI behavior and potentially varies depending on symptom severity. Besides, thyroid hormones are likely related to emotion dysregulation since thyroid receptors located on limbic structures are relevant for mood regulation (Bauer & Whybrow, 2001). Moreover, it needs to be mentioned that most thyroid markers in the NSSI group were in the euthyroid range, meaning that thyroid markers differed significantly on a statistical level but not necessarily on a clinical level. While we have argued that these differences may partly be traced back to fixed individual setpoints, which tend to be stable over lifetime (Medici et al., 2015), the clinical relevance of altered endocrinological markers needs to be further investigated in future research. In addition, replications are needed to confirm and expand our findings as **Study 3** is one of the first studies on HPT axis functioning in adolescent NSSI patients. Here, it may also be helpful to implement naturalistic approaches, such as ecological momentary assessments, to increase the external validity of the current findings[8]. Using naturalistic approaches may further allow for a comprehensive investigation of stress exposure and HPA axis functioning by assessing biological states before, during and after NSSI episodes.

[8] Ecological momentary assessment (EMA) has been defined as a series of repeated measures to investigate current affective, behavioral and contextual experiences or physiological processes while participants engage in normal daily activities (Santangelo et al., 2014).

Directions for Future Research

Future studies may build on the current set of studies to further increase the validity of the reported results. First, as the studies were designed cross-sectionally, findings do not allow for final conclusions on whether altered endocrinological markers reinforce psychopathological characteristics and vice versa. Correspondingly, longitudinal designs are needed to disentangle effects of age, illness duration, and illness severity across the lifespan. For instance, and as hypothesized by Kaess et al. (2021), it seems likely that endocrinological alterations differ between young NSSI patients at the onset of various mental disorders and older NSSI patients with comorbid, longer-lasting BPD. Longitudinal approaches seems further relevant to investigate the course of development, i.e. overlaps with regard to altered endocrinological functioning and BPD chronification, and may additionally enable investigating aspects such as resilience, protective factors and therapeutic interventions, hence circumstances leading to improved psychosocial health. Here, we recommend that future research integrates experimental therapeutic interventions, such as disorder-specific treatments focusing on emotion dysregulation in BPD, to scrutinize the potentially predictive value of endocrine markers. Besides, based on longitudinal approaches it may be investigated how improvement in mental health condition affects endocrine markers and vice versa. Methodological limitations associated with singular endocrinological measures may additionally be overcome by assessing dynamic and repeated endocrinological measures, for instance based on psychosocial challenges. In this context, we recommend to recruit sufficiently large samples to ensure ample statistical power and to enable respective subgroup analyses. Subgroup analyses seem particularly important as the respective samples are characterized by high heterogeneity, which is why different comorbidity statuses need to be contrasted with regard to different endocrinological profiles as shown exemplarily in **Study 1**.

Another important aspect refers to the question of how adverse childhood experiences affect associations between psychopathology and endocrinological markers. Therefore, examining the impact of childhood adversity in greater detail seems crucial to examine the biosocial theory for BPD (Linehan, 1993) and the temporal framework for NSSI (Kaess et al., 2021) even more thoroughly. Hence, while findings from **Study 2** and **Study 3** indicate higher prevalences of adverse childhood experiences in BPD and NSSI patients of different age groups, the etiological impact has not been investigated sufficiently yet. Moreover, the instruments used in **Study 2** and **Study 3** were based on retrospective self-report, which may

be prone to error, for instance due exaggeration or social desirability bias. We therefore recommend to apply both self- and external assessments in future research to examine the impact of adverse childhood experiences as comprehensively as possible. Examining the detrimental consequences of adverse childhood experiences may further be achieved through prospective research designs, hence studies investigating biological markers preceding BPD and NSSI onset, to track temporal changes across development more closely.

Lastly, the present work is limited by its predominant focus on female participants as **Study 2** and **Study 3** exclusively investigated female participants and meta-analyses conducted in **Study 1** mainly included primary studies based on female samples. Yet, investigating potential gender differences seems especially important as endocrine disorders are distributed differently between the genders and as BPD and NSSI are diagnosed more frequently in females (Jacobson & Gould, 2007; Skodol & Bender, 2003; Widiger & Weissman, 1991). Thus, future studies should increasingly focus on mixed samples or fully male samples to examine the impact of gender on endocrinological markers and psychopathology more closely.

Clinical Implications

Next to the theoretical considerations mentioned above, three key clinical implications follow from the current dissertation. First, and owing to presumably altered endocrinological profiles in BPD and NSSI as potential correlates for dysfunctional stress regulation, treatments should address stress regulation capacities and aim at improving an individual's capacities. Besides, altered cortisol and thyroid levels need to be monitored closely in the corresponding patient groups, as such alterations may potentially characterize certain BPD and NSSI subgroups. Correspondingly, stratification of the corresponding samples may eventually allow for drawing conclusions on differential developmental courses and probable treatment responses. This aspect seems crucial as abnormal endocrinological functioning also relates to various health issues, such as metabolic discomfort, inflammation, and neuropsychiatric dysfunctions. And, as research has shown that non-remission of BPD is associated with a heightened risk of chronic physical conditions, making poor health-related lifestyle choices and requiring costly forms of medical services (Zanarini et al., 2004), health problems associated with altered endocrinological functioning need to be monitored particularly closely. Thus, and given that future studies can replicate the current findings, a

comprehensive biomarker assessment in BPD and NSSI patients may potentially be considered a valuable supplement to established diagnostic tools.

The second clinical implication relates to the importance of preventive interventions as our findings indicate that developmental factors, such as early life stress, affect endocrinological functioning significantly. Conversely, one may assume that improved mental health conditions are paralleled by endocrinological alterations. If this assumption can be confirmed by future research, then carefully selected endocrinological markers may provide a feasible option to evaluate existing therapeutic interventions. Hence, if therapeutic interventions lead to endocrinological alterations and if these alterations correspond to clinical improvements, then these therapeutic interventions should be made more available in order to help patients coping with or potentially even preventing BPD and NSSI chronification. Here, particular attention needs to be paid to sensitivity and specificity of the respective markers as various factors may lead to changes in endocrinological functioning. Besides, it may be particularly worthwhile to investigate associations between endocrinological markers and stress perception to apply the corresponding biomarkers as precisely as possible. For this purpose, endocrinological markers need to be contrasted with other diagnostic tools, such as psychometric instruments and brain imaging techniques, to evaluate the corresponding markers comprehensively.

Lastly, and despite ongoing efforts to investigate BPD and NSSI in adolescence thoroughly, more research is needed to classify the respective clinical and endocrine associations well. As this line of research is closely associated with comprehensive diagnostics and treatment, future research may focus on stratifying BPD and NSSI patients according to their stress regulation capacities and biological profiles to eventually enable personalized treatments. Implementing precise but ample diagnostics as well as comprehensively evaluated, disorder-specific treatments should therefore guide future research on endocrinological profiles in BPD and NSSI patients.

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Hypothalamic-pituitary-adrenal axis functioning in borderline personality disorder: A meta-analysis

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ABSTRACT

Borderline Personality Disorder (BPD) has been associated with altered hypothalamic-pituitary-adrenal (HPA) axis functioning. However, evidence is inconsistent. Therefore, the present series of meta-analyses aimed to quantify HPA axis functioning in BPD patients based on singular and continuous cortisol assessments and measures of reactivity to pharmacological and psychosocial stress. Case-control studies comparing adult BPD patients and healthy and clinical controls were considered for inclusion. The search resulted in 804 publications, of which 37 studies (k = 81; BPD n = 803, controls n = 1092) were included. Analyses were based on random effect models using standardized mean differences. BPD patients displayed elevated continuous cortisol output and blunted cortisol following psychosocial challenges. Singular cortisol assessments and cortisol after pharmacological challenges were not significantly different. Meta-analyses were limited by inconsistent reporting in individual studies and small samples for some comparisons. Due to the debilitating nature of stress-related symptoms in BPD, more research on elevated continuous cortisol output and blunted cortisol responses to psychosocial stress is warranted.

1. Introduction

1.1. Stress reactivity in borderline personality disorder

Borderline Personality Disorder (BPD) is a severe and heterogeneous disorder, which is characterized by affective instability, impulsivity, and interpersonal instability (Leichsenring et al., 2011). Heterogeneity emerges as five out of nine, seemingly dissimilar criteria need to be met for a diagnosis based on the DSM-5 (American Psychiatric Association, 1994). Yet homogeneity prevails when considering the role of stress in both the development and maintenance of the disorder (Kuhlmann et al., 2013). On the one hand, heightened stress exposure early in life has been considered a risk factor for the development of BPD. On the other hand, increased vulnerability and maladaptive responses to stress are generally thought to be reflected by multiple BPD symptoms (Grove et al., 2017). Correspondingly, Zimmerman and Choi-Kain (2009) proposed that stress-related symptoms in BPD can be differentiated based on their chronic or acute nature. Chronic symptoms are considered stable and temperamental features such as dysphoria, intolerance of aloneness, and concerns of abandonment. In contrast, acute symptoms are thought to be short-term responses to stress and tend to remit quickly, such as impulsivity, mood reactivity, and self-injurious behavior (Bourvis et al., 2017). Taken together, both chronic and acute symptoms might relate to stress responsivity, however, the pathophysiology of this altered stress responsivity in BPD remains largely unclear (Wingenfeld et al., 2010).

1.2. The hypothalamic-pituitary-adrenal axis: a major stress response system

One of the primary neurobiological systems related to the regulation of stress is the hypothalamic-pituitary-adrenal (HPA) axis (Lightman, 2008; Mitrovic, 2002) and prior research demonstrated that BPD patients are characterized by "*increased stress vulnerability, disturbed HPA axis functioning and alterations in the size and activation of structures involved in central stress regulation*" (Kuhlmann et al., 2013, p. 130). The

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HPA axis regulates stress responses through feedforward and feedback mechanisms (Morris et al., 2012). The feedforward mechanism involves the hypothalamus, which releases corticotropin-releasing hormones (CRH) in response to a stressor. CRH is carried to the anterior pituitary gland. This stimulates the production of adrenocorticotropic hormones (ACTH) in the anterior pituitary gland, which prompts the adrenal cortex to produce the glucocorticoid hormone cortisol (Buitelaar, 2013; Zimmerman and Choi-Kain, 2009). As cortisol secretion follows a diurnal rhythm (Fries et al., 2009), cortisol increases sharply upon awakening and declines over the course of the day (Girshkin et al., 2014). Cortisol has various metabolic functions, such as increasing blood sugar levels and suppressing the immune system (Randall, 2010). However, cortisol also restores homeostasis following exposure to stress through a negative feedback loop. Hence, cortisol downregulates its secretion by inhibiting CRH and ACTH (Mitrovic, 2002; Zimmerman and Choi-Kain, 2009). In essence, both feedforward and feedback loops modulate the HPA axis and consequently impact the individual stress response (Carrasco and van de Kar, 2003).

1.3. Assessing HPA axis functioning in borderline personality disorder

Given its critical role in regulating stress responses, the HPA axis is one of the most thoroughly investigated physiological systems in clinical psychology and psychiatry (Nicolson, 2008). HPA axis activity can be measured based on several methods and assays. In fact, various observational and experimental approaches have been developed to study different components of HPA axis functioning. First, singular cortisol assessments and continuous measurements serve as proxies for spontaneous hormone secretion. Accordingly, saliva and blood[1] samples have commonly been used to assess current cortisol concentrations. Altered cortisol values can be interpreted as a sign of HPA axis dysregulation due to chronic stress or illness (Lupien and Seguin, 2013). Continuous HPA axis measurements further refer to assessments of diurnal or overnight cortisol release and are frequently used to measure cortisol secretion under natural, non-laboratory conditions (Lieb et al., 2004). Continuous cortisol output is typically examined with urinary cortisol or averaged salivary or blood cortisol samples over a period of 12–24 h (Lupien and Seguin, 2013). As cortisol secretion follows a diurnal rhythm, such assessment is a more balanced measure than singular cortisol assessments. Additionally, hair cortisol can be used to assess long-term cortisol secretion (Russell et al., 2012). In short, the method of cortisol measurement varies depending on the period of interest (Morris et al., 2012).

Second, pharmacological manipulations, such as the *dexamethasone suppression test* (DST), enable determination of feedback functioning (Carroll, 1985). As dexamethasone inhibits ACTH secretion, the DST typically also decreases cortisol output, which is why insufficient cortisol suppression indicates a dysregulated feedback response (Phillips et al., 2006). Altered DST results have been reported in a variety of psychiatric disorders (Tajima-Pozo et al., 2013), such as Major Depressive Disorder (MDD), Posttraumatic Stress Disorder (PTSD), and childhood adversity. For instance, Yehuda et al. (2004) demonstrated that PTSD patients display enhanced cortisol suppression while MDD patients were characterized by non-suppression of cortisol. Similarly, Rinne et al. (2002) noticed that the *combined dexamethasone/CRH test* (DEX-CRH) is indicative of trauma history, which has been considered an etiological factor in BPD patients (Ball and Links, 2009; Infurna et al., 2015). For a general overview of stereotypical cortisol patterns in MDD, PTSD and childhood adversity, the interested reader is referred to prior reviews by Baumeister et al. (2014); Morris et al. (2012); Kendall-Tackett (2000), and Koss and Gunnar (2017). Additionally, the following reviews investigated HPA axis functioning separately in PTSD patients (de Kloet et al., 2006; Klaassens et al., 2012; Meewisse et al., 2007) and MDD patients (Belvederi Murri et al., 2014; Burke et al., 2005; Lopez-Duran et al., 2009; Ribeiro et al., 1993). Focusing on BPD in particular, early research utilized pharmacological challenges to investigate HPA axis functioning. For instance, Kontaxakis et al. (1987) reported that BPD patients show a rate of cortisol non-suppression comparable to patients with MDD. In contrast, De la Fuente and Mendlewicz (1996) as well as Lahmeyer et al. (1988) demonstrated greater cortisol non-suppression in patients with MDD compared to those with BPD. Yet findings from these studies should be interpreted with caution since different cut-off values defining non-suppression were applied[2]. Other studies reported greater cortisol non-suppression in BPD patients compared to clinical controls (Baxter et al., 1984; Soloff et al., 1982). However, these controls were often poorly characterized questioning the specificity of cortisol non-suppression in BPD. In brief, findings from these studies suggest abnormal cortisol suppression in BPD but evidence is inconsistent. Although partly attributable to miscellaneous definitions of cortisol non-suppression and obsolete diagnostic criteria, it is currently unclear if cortisol non-suppression following pharmacological challenges can be considered a BPD-specific biomarker (Chanen and Kaess, 2012). In order to resolve this issue, a systematic meta-analytic investigation, quantifying the existing evidence, is warranted.

Third, psychosocial stress tests are crucial to examine reactivity to experimental and acute real-life stressors. For instance, reactivity to interpersonal stressors is commonly investigated with the *Trier Social Stress Test* (TSST; Kirschbaum et al., 1993), which consists of delivering a speech and performing a mental arithmetic task in front of an audience. Typically, cortisol is measured before stressor onset (baseline), up to 25 min after stressor onset (stress response), and more than 25 min after stressor onset (recovery from stress). Corresponding HPA axis abnormalities likely indicate dysfunctional stress regulation capacities and concur with chronic and especially acute BPD symptoms. The finding that psychosocial functioning is often inadequate in BPD patients (Zanarini et al., 2006) suggests that these patients also display increased cortisol responses to psychosocial challenges. Support for increased cortisol levels in BPD patients has been provided by initial studies (e.g., Simeon et al., 2007; Walter et al., 2008). However, these studies often suffered from small samples sizes and provide only limited evidence for abnormal HPA axis responses to psychosocial stressors in BPD patients.

1.4. Objectives

In summary, existing research suggests enhanced basal and stimulated cortisol release in BPD (Wingenfeld et al., 2010). However, results from individual studies were often contradictory (Scott et al., 2013). And, albeit earlier reviews summarized studies on HPA axis activity in BPD qualitatively (Wingenfeld et al., 2010; Zimmerman and Choi-Kain, 2009), a quantitative review of the existing evidence is missing. Such an analysis appears highly relevant in order to overcome limitations inherent to individual studies and to develop a thorough understanding of the endocrinological system underlying stress regulation capacities in patients with BPD. Therefore, the present series of meta-analyses examined case-control studies focusing on cortisol activity among BPD patients as compared to healthy controls (HC) as well as clinical controls (CC) with MDD or other Personality Disorders (PD). Separate analyses were conducted to address different facets of HPA axis functioning in BPD using four prevailing paradigms, i.e. singular and continuous cortisol assessments, pharmacological challenges, and psychosocial stress tests. Based on previous reviews (Wingenfeld et al., 2010; Zimmerman and Choi-Kain, 2009), it was expected that BPD patients

[1] cortisol can be measured in blood based on serum or plasma assays.

[2] to give one example, Beeber et al. (1984) and Soloff et al. (1982) used a cut-off of 4 μg/dl while De la Fuente and Mendlewicz (1996) as well as Lahmeyer et al. (1988) used a cut-off of 5 μg/dl.

display enhanced cortisol in singular and continuous assessments, non-suppression of cortisol following pharmacological challenges, and increased cortisol responses to psychosocial stress. Further, a range of potential covariates, such as sex ratio and average age of BPD patients as well as study quality, were subject to meta-regressions to facilitate interpretation of the results. Those factors were chosen as prior reviews suggested that they might either impact HPA axis functioning in BPD patients in particular or comparisons between experimental groups more generally.

2. Methods

2.1. Protocol and registration

This meta-analysis was preregistered through a web-based protocol on the 'International Prospective Register of Systematic Reviews' by the Centre for Reviews and Dissemination (PROSPERO; registration number CRD42017062312). The guidelines of the PRISMA statement (Liberati et al., 2009; Moher et al., 2015) were used as a framework. The protocol was published on April 16, 2017 and review stages were updated promptly. Title, keywords, hand-search procedures, and planned analyses were adjusted during the review process. These adjustments were required as the initial selection of journals did not yield satisfactory findings and as the analyses had to be adjusted to the characteristics of the included studies, such as multiple relevant comparisons within one experimental study. Both the initial and the adapted version can be inspected on PROSPERO (https://tinyurl.com/yawpgt7w).

2.2. Eligibility criteria

Empirical studies other than case reports were included if (1) formally diagnosed[3] BPD patients were compared to HC or CC above 18 years of age, (2) HPA axis-related dependent variables such as CRH, ACTH, or cortisol were studied, (3) singular or continuous indices of HPA axis activity or HPA axis responses to pharmacological (i.e. DST and DEX-CRH) or psychosocial challenges (e.g., TSST) were measured, and if (4) sufficient information, such as group means and standard deviations, were disclosed. Studies were excluded if they (5) were published in abstract form only, (6) did not contain primary data (e.g., systematic reviews, meta-analyses, or editorials), (7) reported on cortisol assessments in PDs in general, (8) included individuals with endocrine disorders[4], and when (9) data for BPD patients were not reported separately from other participants. Corresponding authors were contacted in cases of uncertainty. Studies, that were published between 1980[5]-2017, were considered eligible if written in English, Dutch, or German.

2.3. Information sources

The search was developed and conducted by the first author. Published studies were identified by searching the electronic databases PsycINFO, MEDLINE, Embase, Scopus, and Web of Science. The following restrictions and filters were implemented: PsycINFO was searched for studies reporting on adult human participants; MEDLINE was searched for articles in English, Dutch, and German language reporting on human participants; Embase was searched for studies using human adults; Scopus was restricted to English, Dutch and German language; and Web of Science was searched for articles written in English, German, and other languages not specified. Moreover, unpublished studies were identified through the ProQuest Dissertations & Theses database (1980–2017). Repeated extractions were avoided by applying deduplicate tools before collecting the articles.[6] The following journals were hand-searched for matching publications: *'Psychoneuroendocrinology'*(1980–2017), *'Journal of Personality Disorders'*(1987–2017), *'Journal of Neuroendocrinology'* (1989–2017), and *'Hormones and Behavior'*(1980–2017). Further, reference lists of prior reviews on HPA axis functioning in BPD were checked (Wingenfeld et al., 2010; Zimmerman and Choi-Kain, 2009). Also, the Clinical Trials database (http://clinicaltrials.gov/) was searched for on-going trials, and experts in the field were contacted to determine if they had unpublished data available to share.[7]

2.4. Search

Prior to formulating the protocol, a pilot search was conducted to ensure that no systematic review or meta-analysis pertaining to the research questions had been previously published or registered. The Cochrane Database for Systematic Reviews, PROSPERO, PubMed, and PsycINFO were used as resources. Next, we formulated a search string for searching PsycINFO. The first component consisted of "borderline personality disorder", "emotionally unstable personality disorder", or "borderline patient*". The second component included "HPA axis", "cortisol", "hormone*", and synonyms. The full search strategy including hits per search term for PsycINFO is provided in Appendix A. Similar search terms were used for all databases.

2.5. Study selection

The eligibility assessment was performed by five reviewers (AEA, ED, GT, LT, PD[8]) in a blinded and standardized manner so that two reviewers rated each article. Immediate agreement was reached in 91% of the cases (inter-rater reliability: Cohen's $\kappa = .67$). Remaining disagreements were resolved by consensus. When no agreement could be reached, a sixth reviewer made a final decision (EF). Prior to full-text evaluation of the articles, titles and abstracts were screened based on the in- and exclusion criteria outlined above. Full texts were considered for inclusion if all criteria were met or likely met, hence if abstracts indicated that all criteria were satisfied in the corresponding articles. Articles were included in the quantitative synthesis if all inclusion criteria were reported in the article or if corresponding authors provided missing details so that all criteria could be considered satisfied.

2.6. Data collection process

A digital data extraction sheet was developed (ED, AA) based on the recommendations by Tacconelli (2010). The extraction sheet was pilot-tested on seven included, randomly chosen studies (AEA, GT, LT, PD) and refined accordingly (ED). Five reviewers independently extracted data from the included studies (AEA, ED, GT, LT, PD) so that all extractions were completed in duplicate. Disagreements were resolved by discussion between reviewers. Duplicate reports were removed when identical samples were described (De la Fuente et al., 2002b; De la Fuente and Mendlewicz, 1996; Ehrenthal et al., 2018; Kahl et al.,

[3] diagnoses had to be based on validated diagnostic instruments such as the *Structured Clinical Interview for DSM-IV Axis II Disorders* (SCID-II; First et al., 1997) or the *Revised Diagnostic Interview for Borderlines* (DIB-R; Zanarini et al., 1989).

[4] in particular, studies focusing on individuals suffering from Cushing's disease, Addison's disease, and Chronic Fatigue Syndrome were excluded since abnormal neuroendocrine functioning is characteristic for these disorders.

[5] BPD was first introduced as a disorder in the DSM-III in 1980 (American Psychiatric Association, 1994).

[6] the respective tools in each database and the deduplicate tool in Endnote were used. The remaining duplicates were removed manually.

[7] Prof. Katja Wingenfeld and Prof. Lois W. Choi-Kain were contacted to retrieve potential information of further studies.

[8] full names of all reviewers are listed in the *Acknowledgements* section. The remaining reviewers are listed as co-authors.

2006a). When multiple samples were compared within one study, the largest sample was chosen.[9] If multiple measurements were taken during the day, the measurements closest to 8 A M and 4 P M were taken as morning and afternoon measurements. In line with previous research (Dickerson and Kemeny, 2004), we defined psychosocial stressors as non-metabolically demanding tasks, which excluded physical stressors, physical-psychological stressor combinations and studies involving pharmacological challenges. Accordingly, we only included acute psychological laboratory stressors[10] such as cognitive tasks, public speaking tasks, and emotion induction procedures. For psychosocial stress tests, the measurement before stressor onset was taken as baseline measure, the measurement up to 25 min after stressor onset as stress measure, and the measurement more than 25 min after stressor onset as recovery measure, as recommended by Burke et al. (2005). Further, a web-based digitizer (Rohatgi, 2012) was used to extract means and standard deviations for studies that only reported relevant statistics based on visual illustrations. When labels were missing from figures, we assumed that means and standard errors were reported. Standard errors were converted to standard deviations based on the following formula: $SD = SEM\ x\ \sqrt{N}$ as suggested by Zakzanis (2001). Similar to Dickerson and Kemeny (2004), a conservative effect size (ES) of Hedges' $g = 0.00$ was chosen if *'no significant changes'* were reported without additional information.

2.7. Data items

Information was extracted from each included trial on (1) *general information and identifying features of the study*, i.e. the full reference, year of publication, and publication status, (2) *study characteristics* such as procedures used to match participants (3) *participant characteristics*, i.e. sample sizes, sex ratio, average age, average body mass index (BMI), medication use, (4) *study design*, i.e. time of sampling, sampling material used, and details on singular or continuous assessments, as well as pharmacological and psychosocial stress testing, (5) *results*, i.e. HPA axis-related findings and corresponding statistics, as well as (6) the *quality assessment* (see *2.8 Risk of bias in individual studies* for a detailed description). Besides, a range of variables were examined as potential moderators. First, age was included as cortisol typically increases with age but as age might also impact acute stress reactivity (Otte et al., 2005). Second, sex was included as males and females often display differential responses to experimental stressors, for instance due to female reproductive hormones and contraceptive medication (Nicolson, 2008). Third, studies using medication wash-out periods and unmedicated patients were compared to studies with medicated patients or studies not reporting on medication use. Fourth, differential effects of psychosocial challenges were addressed, as past research indicated that various psychosocial challenges impact clinical and healthy populations differently (Dickerson and Kemeny, 2004; Ribeiro et al., 1993). In particular, psychosocial challenges were coded as TSST, Conflict Discussion, Emotion Induction, or Cyberball. Fifth, various assessment methods were evaluated to compare endocrinological differences in diurnal rhythms and assessment types of different body fluids. Material was coded as blood[11] or saliva. Timing of assessment was coded as morning (AM) or afternoon (PM). Lastly, studies were scrutinized based on quality scores and matched participant characteristics to investigate if systematic differences could be ascribed to the methodological rigor of the individual studies. The extraction sheet has been published as part of the corresponding Open Science Foundation (OSF) project (Drews et al., 2017).

2.8. Risk of bias in individual studies

To measure risk of bias, five reviewers (AEA, ED, GT, LT, PD) independently assessed study quality based on an adjusted version of the quality tool for studies on HPA axis functioning by Tak et al. (2011). The original quality tool includes nine items related to three key domains in clinical neuroendocrine research, i.e. selection of participants, measurement of HPA axis, and assessment of confounders (Tak et al., 2009). For the current meta-analysis, two items were adjusted and one was reworded to evaluate the quality of studies comparing BPD patients to controls[12]. Two additional items assessed the quality of the experimental design. One item assessed manipulation checks. The other item assessed if subjective stress levels were studied. Quality scores were awarded depending on the design of the primary study. Hence, studies using singular and continuous cortisol assessments were awarded a maximum score of 18 points. Studies assessing cortisol after pharmacological challenges received a maximum score of 20 points. Further, studies focusing on psychosocial challenges were awarded a maximum of 22 points to additionally examine if measures of subjective stress levels were included. For meta-regressions, quality scores based on singular cortisol assessments were used for all studies. The quality assessment is shown in Appendix B.

2.9. Statistical analyses

In total, ten meta-analyses were conducted to compare BPD patients to HC, MDD patients, and PD patients, respectively. To account for small sample sizes, Hedges' *g* (Hedges, 1982) was chosen as weighted measure of individual and combined ES to examine cortisol differences between BPD patients and controls, as recommended by Klaassens et al. (2012). Individual and combined ES were calculated using *Open Meta Analyst* (OMA; Wallace et al., 2012) and *Comprehensive Meta-Analysis* (CMA; Version 3, Biostat, Englewood, NJ, USA). All analyses were based on random effect models. Heterogeneity between studies was measured with the chi-square *Q*-statistic to test the null hypothesis that all variation in effects is due to sampling error. Heterogeneity was further examined with the I^2 index, which indicates the proportion of true variance to observed variance. Generally, I^2 values of 25%, 50%, and 75% correspond to small, moderate, and high levels of heterogeneity (Klaassens et al., 2012). Meta-regressions were calculated for the following potential covariates of study heterogeneity: age (continuous in years), sex (continuous in percentages), assessment time (factorial: AM vs. PM), study quality (continuous in quality points), matched participant characteristics (continuous in number of matched characteristics), sampling material (factorial: blood vs. saliva), medication use (factorial: medicated and medications not reported vs. unmedicated and medication wash-out), and psychosocial challenge (factorial: TSST vs. Conflict Discussion vs. Emotion Induction vs. Cyberball). Meta-regressions were carried out when at least ten

[9] e.g., for the study by Scott et al. (2013), the comparison between BPD participants and the non-trait-matched HC group was chosen.

[10] acute laboratory stressor tasks were defined as *"tasks that lasted 60 minutes or less and did not serve a function outside the laboratory setting; this excluded extended stressor challenges, chronic stressor studies (e.g., caregiving), and naturalistic stressors"* (e.g., class examinations; Dickerson and Kemeny, 2004, p. 360). Accordingly, we included studies using the TSST, Emotion Induction procedures, Conflict Discussions, and the Cyberball paradigm for the comparison on psychosocial challenges.

[11] the distinction between serum and plasma was not consistently reported in the primary studies. Meta-regressions comparing plasma and serum cortisol for studies included in the current set of meta-analyses indicated no systematic differences between these types of blood samples (all $p \geq .328$).

[12] the first item was adjusted to the current target population of BPD patients. The second item was modified so that the recruitment of control participants could be examined. The fourth item was changed to assess the absence of endocrine disorders instead of disease characteristics. These adjustments were deemed necessary as the initial quality tool has been developed to examine HPA axis functioning in somatic disorders (Tak et al., 2011), which are investigated differently in neuroendocrine research than mental disorders such as BPD.

studies[13] within one meta-analytic comparison reported on the potential covariate[14]. Consequently, meta-regressions are solely reported for studies comparing BPD to HC based on singular cortisol assessments and cortisol assessments during psychosocial challenges. Each covariate was tested using meta-regression with a single covariate at a time in OMA.

2.10. Risk of bias across studies

Publication bias was examined by inspecting funnel plots for all comparisons based on three or more studies. Further, publication bias was formally tested based on Egger's test, where the standard normal deviate is regressed on precision, which is defined as the inverse of the standard error (Rothstein et al., 2006). Biased ES estimates were further investigated with Duval and Tweedie's trim and fill procedure (Duval and Tweedie, 2000), which calculates the effect of potential data censoring including publication bias on the outcome of the meta-analysis. Publication bias was examined in CMA.

3. Results

3.1. Study selection

The search in PsycINFO, MEDLINE, Embase, Scopus, Web of Science, and the ProQuest Dissertations & Theses database yielded 804 citations. After removing duplicates, 502 publications remained of which titles and abstracts were screened. One hundred and thirty-five publications did not report on group comparisons between BPD and HC or CC above 18 years of age based on case-control designs, 48 publications did not contain HPA axis-related dependent variables such as ACTH, CRH, or cortisol, 38 publications were only published in abstract form, 172 publications did not contain primary data, 22 publications did not report outcomes separately for BPD patients and other participants, two publications were published in other languages than English, German, or Dutch, and one publication reported on HPA axis assessments in various PDs rather than in BPD patients specifically. Full texts of the remaining 84 publications were examined in greater detail. Of those, 15 publications did not report on group comparisons between BPD and HC or CC subjects above 18 years of age based on case-control designs, 15 publications reported insufficient statistical information, four publications reported on HPA axis assessments in PDs but not in BPD patients in particular, two studies were only published as abstracts, one publication did not contain HPA axis-related dependent variables, and one publication reported on individuals with neuroendocrine disorders. In particular, the studies by Carroll et al. (1981) and Soloff et al. (1982) could not be included since these publications do not report on case-control designs. Besides, the following publications could not be included as relevant statistics were missing: Baxter et al. (1984); Grossman et al. (2003); Rinne et al. (2002), and Sternbach et al. (1983). Unfortunately, none of the corresponding authors could provide data or missing details. Further, the study by Kaess et al. (2017) could not be included due to its focus on adolescents, which has been defined as exclusion criterion under *2.2 Eligibility criteria*. Lastly, the publication by Dettenborn et al. (2016) principally matches all inclusion criteria, however, no other publication reported on hair cortisol in adult BPD patients. Therefore, the study could not be compared to other studies based on meta-analytic techniques. In case of uncertainty, corresponding authors were contacted and studies were included if authors provided the requested data or if missing details could be retrieved with the digitizer. The remaining 37 publications were included in the quantitative synthesis. The study selection procedure is illustrated in Fig. 1.

3.2. Study characteristics

All 37 studies included in the current series of meta-analyses were case-control studies published in English language. These studies contained 81 comparisons.[15] Forty-three publications reported on singular cortisol assessments, eight publications additionally reported on cortisol comparisons following pharmacological challenges, and 13 publications also reported on cortisol comparisons based on psychosocial stress tests.[16] Five publications reported on continuous cortisol assessments. In total, $n = 803$ BPD patients were compared to $n = 1092$ controls. Thirty-four studies compared BPD patients ($n = 758$) to HC ($n = 902$), seven studies compared BPD patients ($n = 105$) to MDD patients ($n = 113$), and four studies compared BPD patients ($n = 72$) to patients with other PDs ($n = 77$). Overall, 81 ES were computed with each study contributing an average of 2.2 ES. Taken all participants together, most BPD patients were female (83%) and the average age was 29.2 years (range: 18–43). The average BMI of all participating individuals was 24.6 (range: 22–27). However, 20 studies did not report on average BMI of participants. Regarding medication use, 15 studies involved washout periods, 10 studies included participants taking both endocrine and non-endocrine medications, one study only included non-endocrine medications, and five studies did not include participants taking medications. The impact of endocrine medications was not specified in five studies and one study did not report on medication use. As illustrated in Table 1, most cortisol measures were based on saliva ($k = 14$), plasma ($k = 13$), or serum ($k = 8$). For one study, it was not mentioned whether serum or plasma cortisol was used and two studies examined urine cortisol (Simeon et al., 2007; Wingenfeld et al., 2007). Lastly, most cortisol samples were collected in the morning ($k = 21$), while the remaining samples were either taken in the afternoon ($k = 15$) or during night-time ($k = 1$).

3.3. Risk of bias within studies

Quality was assessed as related to selection of participants, quantification of HPA axis function, control for confounding, and experimental HPA axis designs. On average, publications reporting on singular cortisol assessments received a quality score of 11 out of 18 (range: 5–16). Studies using experimental designs were scored 12 out of 22 on average (range: 5–19). Average scores for the different sections of the quality assessment were approximately similar. Hence, studies received an average score of 5/8 points for participant selection, an average score of 4/6 points for quantification of HPA axis function, an average score of 2/4 points for assessment and control for confounders, and an average score of 2/4 points for experimental designs. It should be noted, however, that only a limited number of studies ($k = 4$) reported on blinding of HPA axis assessors. The detailed quality ratings for the individual studies, grouped by paradigm, can be found in Appendix C.

[13] i.e., ten studies focusing on singular or continuous cortisol assessments, pharmacological challenges, or psychosocial challenges, respectively.

[14] for example, quality points for studies examining singular cortisol assessments in BPD patients and HC were analyzed based on a meta-regression because quality points existed for at least ten studies within this meta-analytic comparison.

[15] the following articles included multiple comparison groups: Aleknaviciute et al., 2016; Carvalho Fernando et al., 2012; Deckers et al., 2015; Kahl et al., 2005a, b; Kahl et al., 2006a; Steinberg et al., 1997. As the study by Kahl et al. (2006a) reported duplicate samples for the BPD vs. HC comparison, solely the BPD vs. MDD comparison was included in the current meta-analysis.

[16] it should be noted that the studies reporting on pharmacological challenges and psychosocial stress tests usually included singular cortisol assessments as well. Thereby, the included publications contain 31 comparisons of singular cortisol assessments between BPD patients and HC, five comparisons of singular cortisol assessments between BPD patients and HC, and four comparisons of singular cortisol assessments between BPD and PD patients.

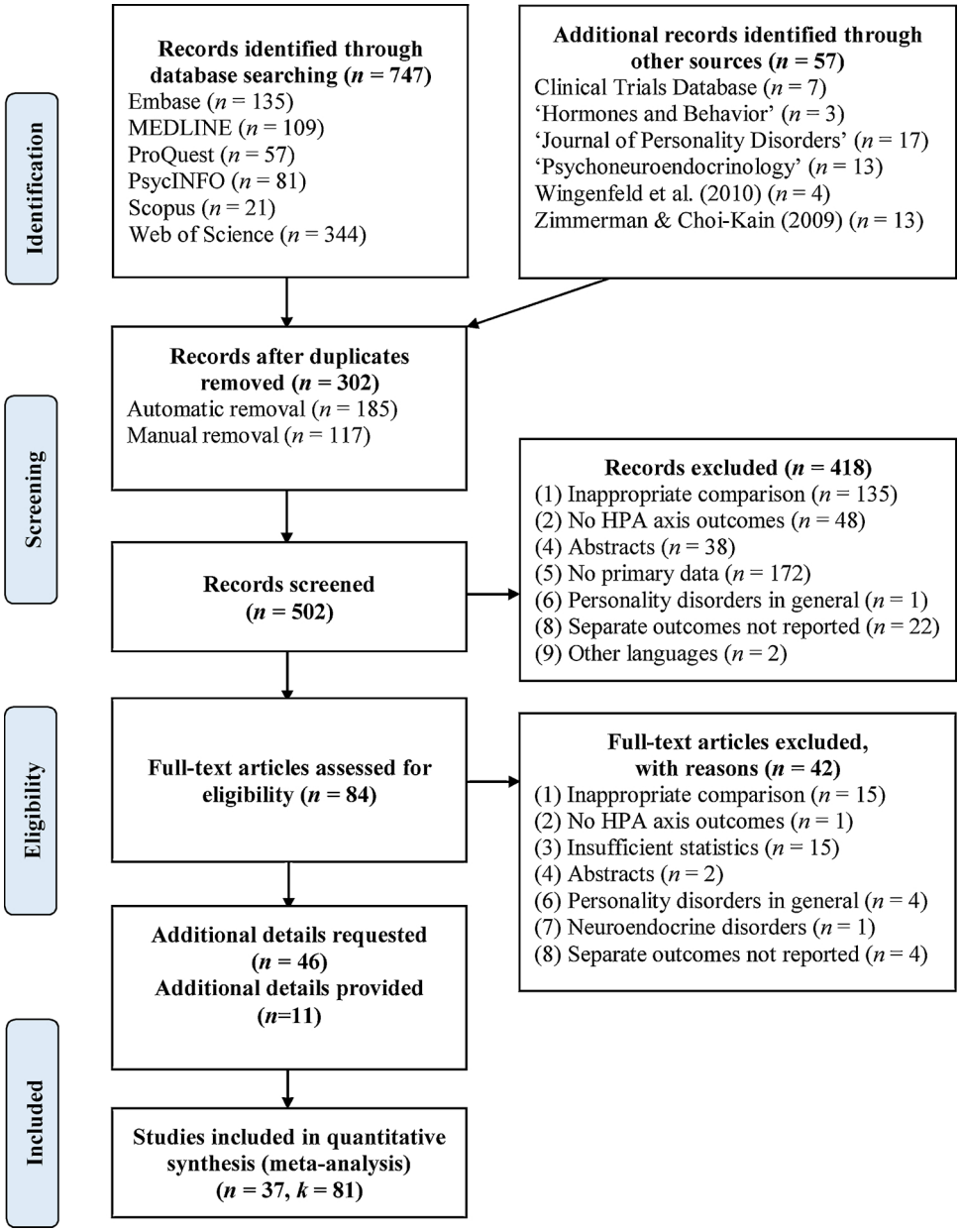

Fig. 1. PRISMA flow diagram illustrating the number of publications identified and the number of publications that were in- and excluded during different stages of the review process.

3.4. Results of individual studies

Outcomes of four separate sets of meta-analyses comparing BPD patients to HC, MDD patients, and PD patients are reported in *3.5 Synthesis of results*. Forest plots are included for singular (BPD vs. HC, BPD vs. MDD, BPD vs. PD) and continuous cortisol assessments (BPD vs. HC), pharmacological challenges (BPD vs. HC, BPD vs. MDD), and psychosocial challenges (BPD vs. HC, BPD vs. PD). Meta-regressions are reported for comparisons of BPD and HC based on singular cortisol assessments and cortisol assessments after psychosocial challenges. The corresponding bubble plots are shown in *Supplement 1*. Further, publication bias was evaluated based on visual inspection of funnel plots, Egger's test, and Duval and Tweedie's trim and fill procedure for studies investigating singular (BPD vs. HC, BPD vs. MDD, BPD vs. PD) and continuous cortisol assessments (BPD vs. HC), pharmacological challenges (BPD vs. HC, BPD vs. MDD), and psychosocial challenges (BPD vs. HC). Funnel plots displaying potential publication bias are presented in *Supplement 1*.

3.5. Synthesis of results

3.5.1. Meta-analyses and heterogeneity estimation for singular cortisol assessments

First, meta-analysis on singular cortisol measures comparing BPD patients (n = 698) and HC (n = 832) showed no significant effect (Hedges' g = 0.37, 95% Confidence Interval (*95% CI*) [-0.11, 0.85], p = . 132, k = 30). The corresponding forest plot is shown in Fig. 2. There was significant heterogeneity (χ^2 = 447.19, p < . 001; I^2 = 94%). Removing one study (Inoue et al., 2015) considerably decreased heterogeneity (χ^2 = 70.81, p < . 001; I^2 = 63%). Taking into account the deviant ES of this study and the high relative weight of the study due to its large control sample (Hedges' g = 6.80, *95% CI* [6.13, 7.47], p < . 001; BPD n = 39, HC n = 229), the study was considered an outlier and removed from all subsequent analyses as recommended by Baker and Jackson (2008). As shown in Fig. 3, the adjusted overall ES was not significant (Hedges' g = 0.12, *95% CI* [-0.08, 0.31], p = . 230; k = 29, BPD n = 659, HC n = 603). Also, no significant difference

Table 1
Characteristics of all comparisons, grouped by publication, as included in the current meta-analysis.

ID	Study		BPD Sample					Control Sample					Assessment		
		Cf.	n	Age	Sex	BMI	Med	n	Age	Sex	BMI	Type	Time	Paradigm	Quality
1.1	Aleknaviciute et al., 2016	HC	26	29.2	100	24.50	0	35	28.6	100	22.4	Saliva	PM	PSY	15
1.2	Aleknaviciute et al., 2016	PD	26	29.2	100	24.50	0	20	26.1	100	23.5	Saliva	PM	PSY	15
2.1	Beeber et al., 1984	MDD	13	NR	NR	NR	4	10	NR	NR	NR	Serum	PM	PHA	7
3.1	Bromundt et al., 2013	HC	14	30.1	100	26.7	3	10	25.7	100	21.4	Saliva	AM	CONT	8
4.1	Carrasco et al., 2003	PD	14	NR	NR	NR	1	10	NR	NR	NR	Plasma	AM	SING	5
5.1	Carrasco et al., 2007	HC	32	30.6	59	NR	1	18	29.7	61	NR	Plasma	AM	PHA	12
6.1	Carvalho Fernando et al., 2012	HC	24	26.9	96	24	4	41	33	68	23.7	Saliva	AM	PHA	14
6.2	Carvalho Fernando et al., 2012	MDD	24	26.9	96	24	4	33	33.4	58	23.6	Saliva	AM	PHA	16
7.1	Carvalho Fernando et al., 2013	HC	32	27.9	100	24.7	3	32	29.5	100	23.3	Saliva	PM	SING	16
8.1	De la Fuente et al., 2002a	MDD	20	32.4	70	NR	1	20	35.8	75	NR	Plasma	PM	PHA	10
9.1	Deckers et al., 2015	HC	22	31.4	100	NR	3	24	28.6	100	NR	Saliva	PM	PSY	13
9.2	Deckers et al., 2015	PD	22	31.4	100	NR	3	23	31.9	100	NR	Saliva	PM	PSY	13
10.1	Feliu-Soler et al., 2013	HC	35	30.2	91	24.5	3	15	30.6	87	22.9	Saliva	PM	PSY	14
11.1	Garbutt et al., 1983	HC	15	28	40	NR	1	15	31	40	NR	Serum	AM	SING	11
12.1	Hollander et al., 1994	HC	12	31.2	67	NR	1	15	32	33	NR	Plasma	AM	SING	8
13.1	Inoue et al., 2015	HC	39	24.4	0	23.7	0	229	25.5	0	23.2	Saliva	PM	PSY	14
14.1	Jobst et al., 2016	HC	22	30	100	NR	3	21	29.7	100	NR	Plasma	AM	PSY	11
15.1	Jogems-Kosterman et al., 2007	HC	22	33.2	100	25.8	3	22	35.7	100	24.7	Saliva	AM	SING	8
16.1	Kahl et al., 2005a	HC	16	25.9	100	24.2	4	20	26.1	100	23.1	Serum	AM	SING	7
16.2	Kahl et al., 2005a	MDD	16	25.9	100	24.2	4	10	24.2	100	25.1	Serum	AM	SING	7
17.1	Kahl et al., 2005b	HC	12	26.8	100	23.6	3	20	26.1	100	23.2	Serum	AM	SING	9
17.2	Kahl et al., 2005b	MDD	12	26.8	100	23.6	3	18	31.9	100	24.4	Serum	AM	SING	9
18.1	Kahl et al., 2006a	MDD	16	25.9	100	24.2	4	12	30	100	25.7	Serum	AM	SING	9
19.1	Kahl et al., 2006b	HC	12	26.3	100	25.9	1	12	25.6	100	21.8	Serum	PM	SING	11
20.1	Kontaxakis et al., 1987	MDD	13	26.4	0	NR	2	13	43.4	0	NR	Plasma	PM	PHA	11
21.1	Lee et al., 2012	HC	4	33.3	75	NR	1	8	28.3	38	NR	Plasma	PM	PHA	14
22.1	Lieb et al., 2004	HC	23	28.5	100	63.6*	1	24	28.2	100	65.8*	Saliva	AM	PHA	12
23.1	Lyons-Ruth et al., 2011	HC	16	21.1	100	NR	3	19	22.5	100	NR	Saliva	PM	PSY	11
24.1	Martial et al., 1997	HC	5	NR	100	NR	1	6	NR	100	NR	Serum	AM	SING	11
25.1	Nater et al., 2010	HC	15	32.6	100	24.9	1	17	27.2	100	21.4	Saliva	PM	PSY	15
26.1	Paris et al., 2004	HC	30	27.7	100	NR	0	22	29	100	NR	Blood$^{\nabla}$	AM	SING	9
27.1	Rausch et al., 2015	HC	35	26.5	100	24.9	0	26	26.3	100	22.8	Saliva	AM	SING	14
28.1	Rinne et al., 2000	HC	12	32.5	100	NR	1	9	33.8	100	NR	Plasma	AM	SING	9
29.1	Roepke et al., 2010	HC	31	29	100	26.1	3	30	28	100	21.1	Serum	AM	SING	10
30.1	Scott et al., 2013	HC	33	30.4	100	NR	3	30	22.7	100	NR	Saliva	PM	PSY	14
31.1	Simeon et al., 2007	HC	8	43.4	25	NR	0	11	27.1	45	NR	Plasma	AM	PSY	10
32.1	Simeon et al., 2011	HC	14	35.1	43	NR	1	13	34.5	69	NR	Plasma	AM	PSY	13
33.1	Sinai et al., 2015	HC	92	29.5	100	NR	4	57	39.4	100	NR	Plasma	PM	SING	7
34.1	Steiger et al., 2001	HC	34	24.4	100	22	1	25	24.6	100	NR	Plasma	AM	SING	12
35.1	Steinberg et al., 1997	HC	10	33.6	50	NR	1	11	30.1	45	NR	Plasma	AM	SING	12
35.2	Steinberg et al., 1997	PD	10	33.6	50	NR	1	24	39.3	38	NR	Plasma	AM	SING	12
36.1	Walter et al., 2008$^{\Diamond}$	HC	9	18.7	76	NR	5	12	18.7	76	NR	Saliva	PM	PSY	5
37.1	Wingenfeld et al., 2007$^{\bullet}$	HC	21	28.1	100	24.4	1	24	27.7	100	24.1	Urine	AM/PM	CONT	9

Note. Cf. = comparison group; HC = healthy controls; PD = clinical controls with a Personality Disorder other than Borderline Personality Disorder (BPD); MDD = clinical controls suffering from Major Depressive Disorder; n = sample size. The sex ratio is indicated as percentage of female participants. BMI = body mass index; Med = medication use, whereby the following definitions have been used: 0 = no medication, 1 = medication washout, 2 = only non-endocrine medications, 3 = mixture of endocrine and non-endocrine medications, 4 = medication use unclear, 5 = medication use not reported. Type refers to the sampling material used, hence to blood (plasma/serum), saliva, or urine. For assessment timing, studies marked as AM were carried out before 12 P M; studies marked as PM were carried out after 12 P M. Paradigm refers to the type of cortisol assessment, hence singular cortisol assessments (SING), continuous cortisol assessments (CONT), psychosocial challenges (PSY), and pharmacological challenges (PHA). Reported quality scores are awarded based on singular cortisol assessments used in the individual studies. The full quality ratings are presented in Appendix C. Multiple comparisons within one study were analyzed separately. * Only weight in kg indicated; ∇ Not stated if serum or plasma was analyzed; ◊ Demographic details only reported for total sample; • Overnight cortisol examined as continuous HPA axis measure.

for singular cortisol assessments between BPD (n = 52) and MDD patients (n = 63) was found (Hedges' g < -0.01, *95% CI* [-0.47, 0.46], p = . 996; k = 3). The corresponding forest plot is given in Fig. 4. The Q-statistic was not significant (χ^2 = 2.80, p = . 247; I^2 = 33%). Lastly, cortisol levels based on singular assessments did not differ significantly between BPD patients (n = 72) and PD patients (n = 77; Hedges' g = -0.39, *95% CI* [-0.80, 0.02], p = . 062; k = 4; Fig. 5). Heterogeneity for the combined effect was moderate but nonsignificant according to the Q-statistic (χ^2 = 4.35, p = . 226; I^2 = 32%).

3.5.2. Meta-regressions comparing singular cortisol assessments

Meta-regressions were conducted on age, sex, medication intake, matched participant characteristics, study quality, sampling material, and assessment time (all k = 29). Matched participant characteristics had a significant impact on the main effect reported (β = -.144, *95% CI* [-0.27, -0.02], standard error (*SE*) = .06, p = .023; Fig. S1; Supplement 1). Leaving out the leverage point significantly decreased this estimate (β = -.080, *95% CI* [-0.24, -0.08], *SE* = .08, p = .328). Neither age (β = -.029, *95% CI* [-0.09, 0.03], *SE* = .03, p = .313), nor sex (β = .002, *95% CI* [-0.01, 0.01], *SE* = .01, p = .676), nor medication intake (β = .058, *95% CI* [-0.32, 0.43], *SE* = .19, p = .764), nor study quality (β = -.032, *95% CI* [-0.10, 0.04], *SE* = .03, p = .346), nor sampling material (β = .172, *95% CI* [-0.21, 0.55], *SE* = .19, p = .373), nor assessment time (β = .163, *95% CI* [-0.22, 0.55], *SE* = .20, p = .402) were significant covariates.

3.5.3. Risk of bias across studies focusing on singular cortisol assessments

Publication bias was examined based on visual inspection of funnel plots, Duval and Tweedie's trim and fill procedure as well as Egger's test for comparisons which were based on at least three studies. The funnel

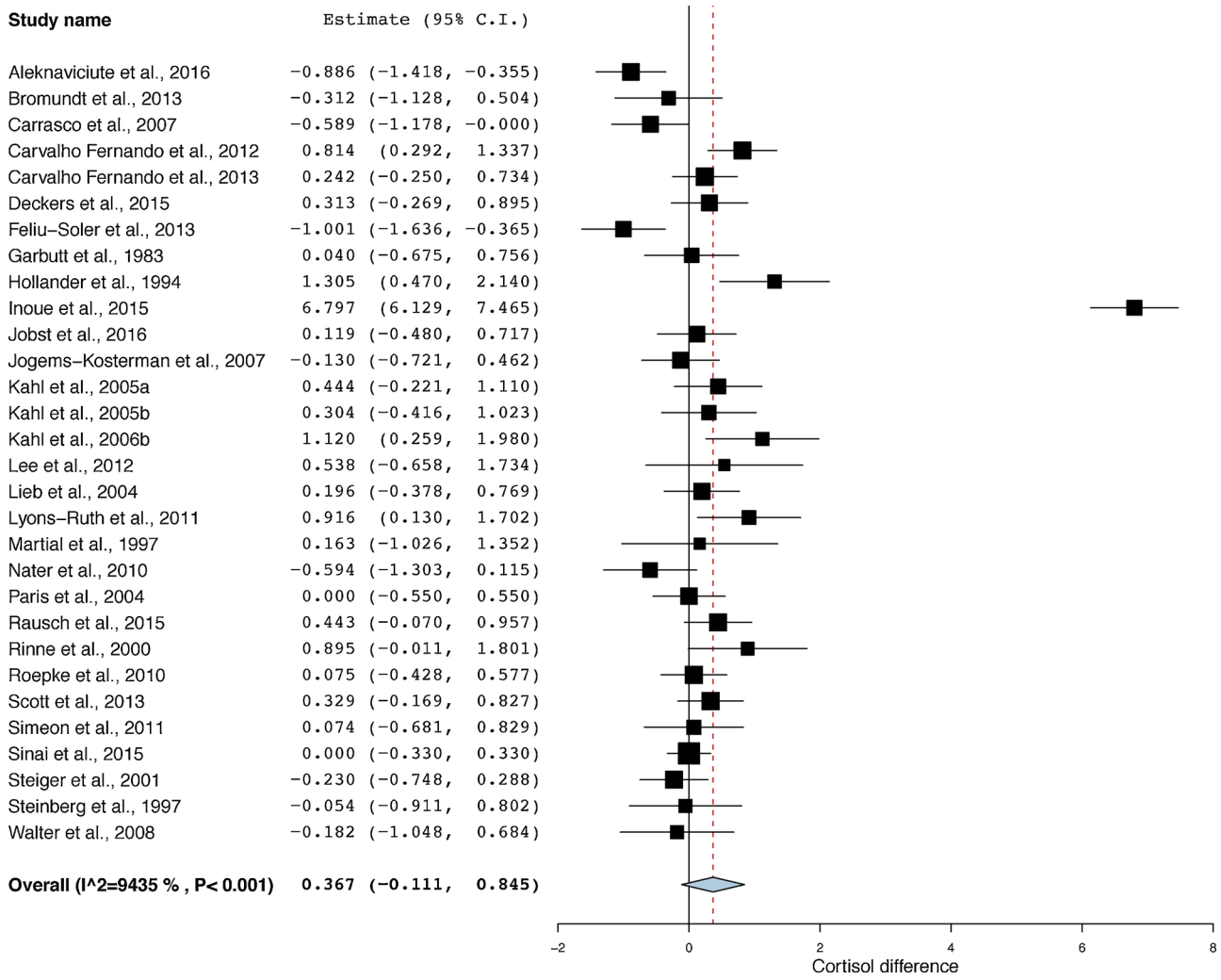

Fig. 2. Forest plot comparing singular cortisol assessments in BPD patients and HC using all available studies.

plot for the comparison of singular cortisol assessments in BPD patients and HC shown in Fig. S2 (Supplement 1) indicated publication bias. The trim and fill procedure yielded six imputed studies and a pooled ES indicating a nonsignificant difference between BPD patients and HC (Hedges' g = -0.05, *95% CI* [-0.25, 0.15]). In contrast, Egger's test did not indicate funnel plot asymmetry (intercept = 1.21, *95% CI* [-1.18, 3.59], p = . 154, k = 29). Publication bias was present for the comparison of singular cortisol assessments in BPD and MDD patients when visually inspecting the funnel plot in Fig. S3 (Supplement 1) and when examining Egger's test (intercept = -6.19, *95% CI* [-15.99, 3.61], p = . 039, k = 3). The trim and fill procedure imputed two additional studies, yielding a decreased pooled ES (Hedges' g = 0.35, *95% CI* [-0.17, 0.87]). Moreover, no publication bias could be detected when inspecting the funnel plot for the comparison of singular cortisol assessments in BPD and PD patients shown in Fig. S4 (Supplement 1). Egger's test did not indicate that the funnel plot was asymmetrical (intercept = 4.13, *95% CI* [-18.22, 26.47], p = . 255, k = 4). The trim and fill procedure imputed one study, leading to a medium pooled ES (Hedges' g = -0.55, *95% CI* [-1.00, -0.09]).

3.5.4. Meta-analyses and heterogeneity estimation for continuous cortisol assessments

Five studies compared continuous cortisol output in BPD and HC. Of those studies, three studies measured salivary cortisol during the day (Bromundt et al., 2013; Carvalho Fernando et al., 2012; Lieb et al., 2004), and two studies measured urinary cortisol either during nighttime (Wingenfeld et al., 2007) or over the course of 24 h (Simeon et al., 2007)[17]. Meta-analysis indicated that BPD patients (n = 90) were characterized by increased continuous cortisol levels compared to HC (n = 110) (Hedges' g = 0.52, *95% CI* [-0.23, 0.81], p < . 001; k = 5; Fig. 6). Heterogeneity was small and nonsignificant (χ^2 = 4.04, p = . 401; I^2 = 1%). None of the studies compared BPD patients to MDD or PD patients based on continuous cortisol assessments.

3.5.5. Risk of bias across studies focusing on continuous cortisol assessments

For the comparison of continuous cortisol assessments, Egger's test demonstrated significant funnel plot asymmetry (intercept = -4.53, *95% CI* [-8.18, -0.87], p = . 029, k = 5). As shown in Fig. S5

[17] for the study by Bromundt et al. (2013), ten cortisol assessments in undefined intervals over the course of the day were included. For the study by Carvalho Fernando et al. (2012), four cortisol samples collected from 0730h to 2000h on the day prior to the DST assessment were selected. For the study by Lieb et al. (2004), seven assessments in 2h intervals over the course of the day were included (called 'total daily cortisol' in the primary study). These cortisol assessments were calculated based on cortisol areas under the curve (AUCs). Wingenfeld et al. (2007) utilized urinary cortisol assessments collected over three consecutive nights (7PM to 7AM) and reported an averaged value. The study by Simeon et al. (2007) took place from 10AM at the first day until 10AM at the second day and reported on the total urinary cortisol output over 24 hours.

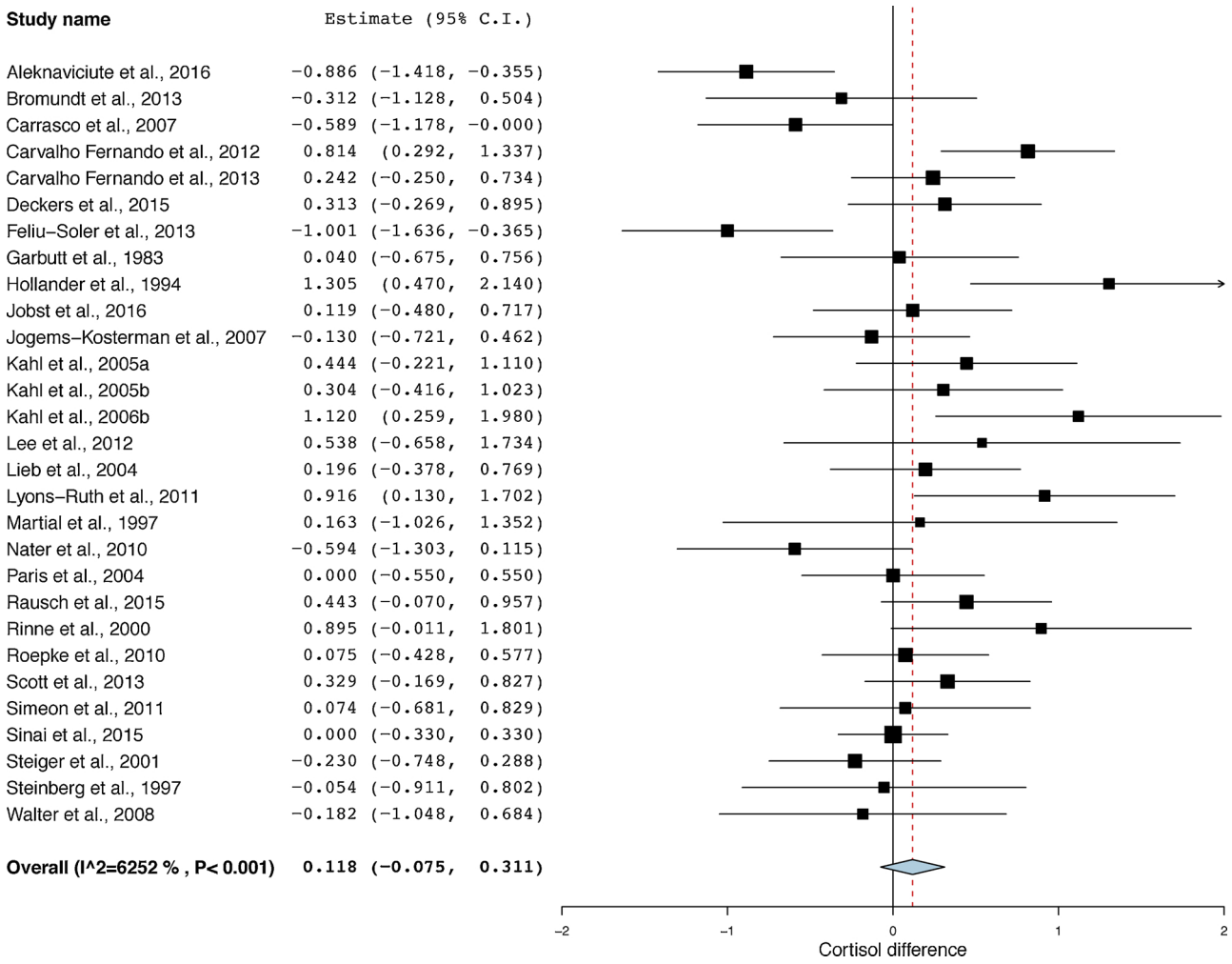

Fig. 3. Forest plot comparing singular cortisol assessments in BPD patients and HC excluding one study (Inoue et al., 2015).

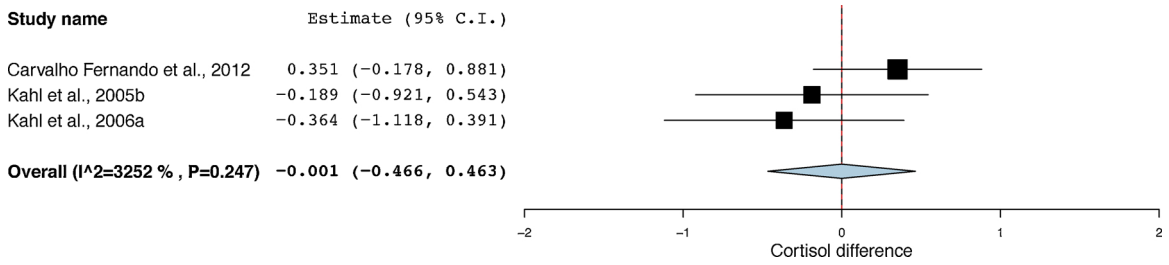

Fig. 4. Forest plot comparing singular cortisol assessments in BPD and MDD patients.

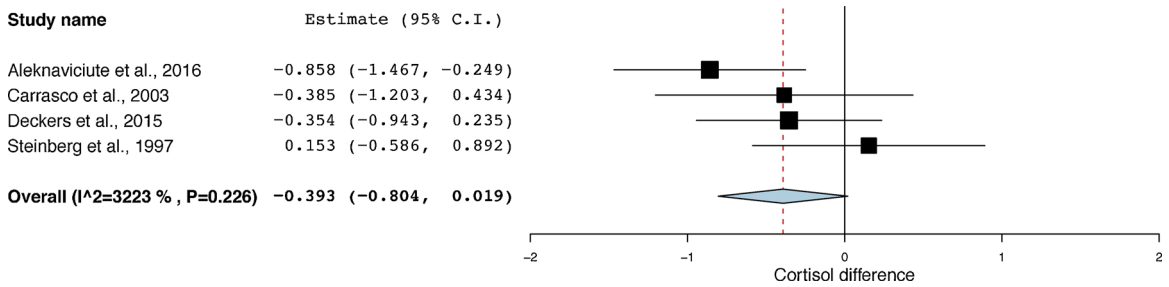

Fig. 5. Forest plot comparing singular cortisol assessments in BPD and patients with other PDs.

(Supplement 1), Duval and Tweedie's trim and fill procedure imputed two studies, yielding a medium ES of Hedges' $g = 0.65$, *95% CI* [0.39, 0.90]).

3.5.6. Meta-analyses and heterogeneity estimation for cortisol assessments based on pharmacological challenges

Cortisol values after pharmacological challenges did not differ

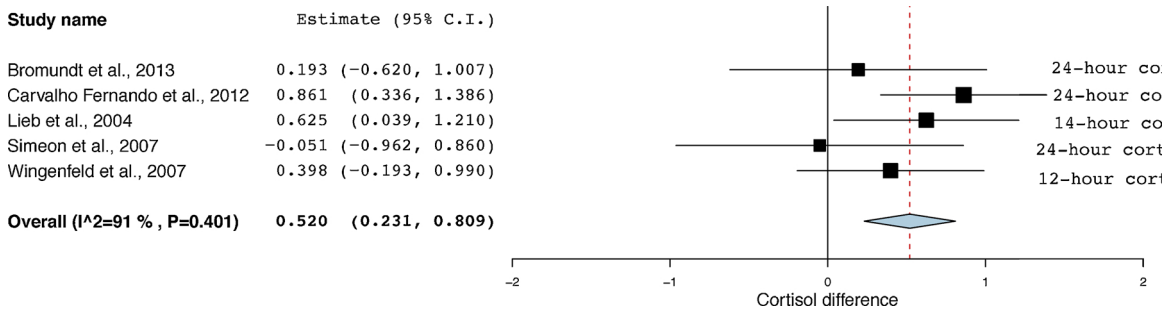

Fig. 6. Forest plot comparing continuous cortisol output in BPD patients and HC. For the studies by Bromundt et al. (2013); Carvalho Fernando et al. (2012) and Lieb et al. (2004), areas under the curve were calculated based on repeated salivary cortisol measures within 14–24 h. Numbers in brackets indicate the amount of saliva samples taken. Simeon et al. (2007) reported 24-hour urinary cortisol measured from 10 A M to 10 A M. Wingenfeld et al. (2007) measured overnight mean urinary cortisol from 7 P M to 7 A M averaged over three consecutive nights.

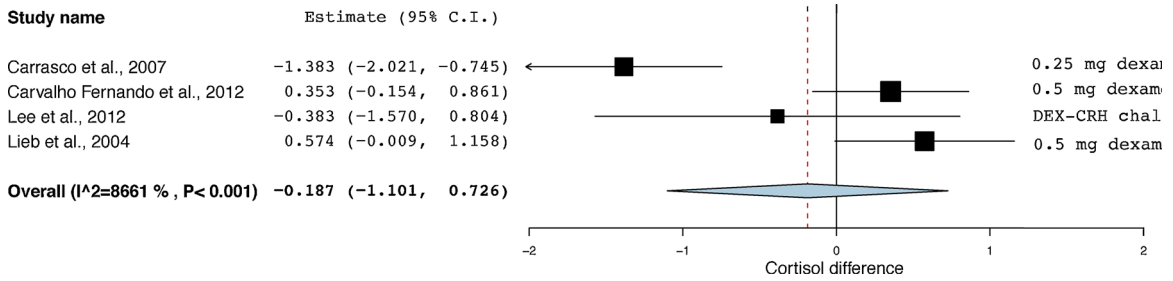

Fig. 7. Forest plot comparing cortisol values after pharmacological challenges in BPD patients and HC. Details on the respective pharmacological challenge are noted on the right side of the figure.

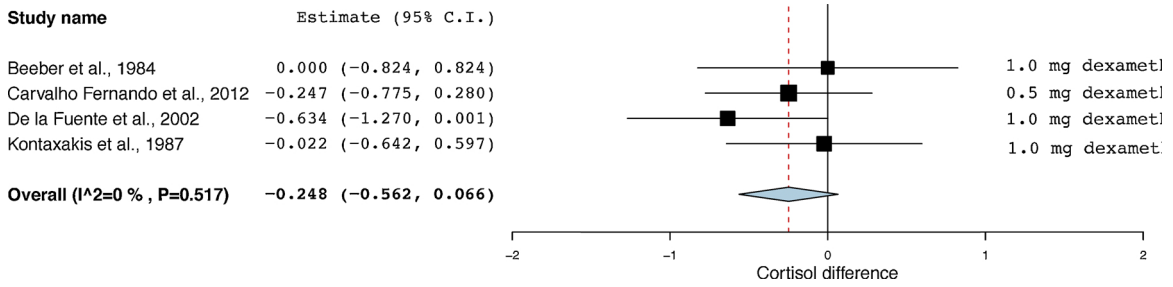

Fig. 8. Forest plot comparing cortisol values after pharmacological challenges in BPD patients and MDD patients. Details on the respective pharmacological challenge are noted on the right side of the figure.

significantly between BPD patients (n = 83) and HC (n = 92; Hedges' g = -0.19, *95% CI* [-1.10, 0.73], p = . 688; k = 4; Fig. 7), however, the combined ES was associated with high heterogeneity (χ^2 = 23.90, p < . 001; I^2 = 87%). Similarly, cortisol levels after pharmacological challenges in BPD patients (n = 77) were not significantly different from those of MDD patients (n = 83; Hedges' g = -0.25, *95% CI* [-0.56, 0.07], p = . 121; k = 3; Fig. 8). The corresponding Q-statistic was nonsignificant (χ^2 = 2.28, p = . 517; I^2 = 0%). Notably, none of the studies compared BPD and PD patients based on pharmacological challenges.

3.5.7. Risk of bias across studies focusing on cortisol assessments based on pharmacological challenges

When examining risk of bias for studies on pharmacological challenges in BPD patients and HC, visual inspection indicated publication bias (Fig. S6; Supplement 1). However, Duval and Tweedie's trim and fill procedure did not impute additional studies. Egger's test was not significant (intercept = -3.46, *95% CI* [-31.61, 24.70], p = . 325, k = 4). As shown in Fig. S7 (Supplement 1), no publication bias was present for the comparison of cortisol after pharmacological challenges in BPD and MDD patients. Duval and Tweedie's trim and fill procedure did not impute additional studies. Egger's test did not indicate asymmetry of the funnel plot (intercept = 1.35, *95% CI* [-14.33, 17.02], p = . 373, k = 4).

3.5.8. Meta-analyses and heterogeneity estimation for cortisol assessments based on psychosocial challenges

When comparing BPD patients to HC, both the response to stress (Hedges' g = -0.32, *95% CI* [-0.57, -0.07], p = . 013; k = 10; BPD n = 200; HC n = 190; Fig. 9) and recovery from stress (Hedges' g = -0.32, *95% CI* [-0.53, -0.11], p = . 003; k = 9; BPD n = 183; HC n = 180; Fig. 10) were associated with significantly blunted cortisol levels in BPD patients. Heterogeneity was small for comparisons focusing on response to stress (χ^2 = 12.64, p = . 180; I^2 = 31%) and recovery from stress (χ^2 = 7.28, p = . 507; I^2 = 0%). Further, cortisol secretion in BPD and PD patients during and after the TSST was compared in two studies (Aleknaviciute et al., 2016; Deckers et al., 2015). Cortisol responses during stress (Hedges' g = -0.80, *95% CI* [-1.61, 0.01], p = . 051; k = 2, BPD n = 48; HC n = 43) and recovery (Hedges' g = -0.74, *95% CI* [-1.30, -0.18], p = . 010; k = 2, BPD n = 48, HC n = 43; Fig. 11) were decreased in BPD compared to PD patients. Heterogeneity for the combined effects was moderate but non-significant according to the Q-statistic (Q-test for stress measure: χ^2 = 3.45, p = . 063; I^2 = 71%; Q-test for recovery measure: χ^2 = 1.70,

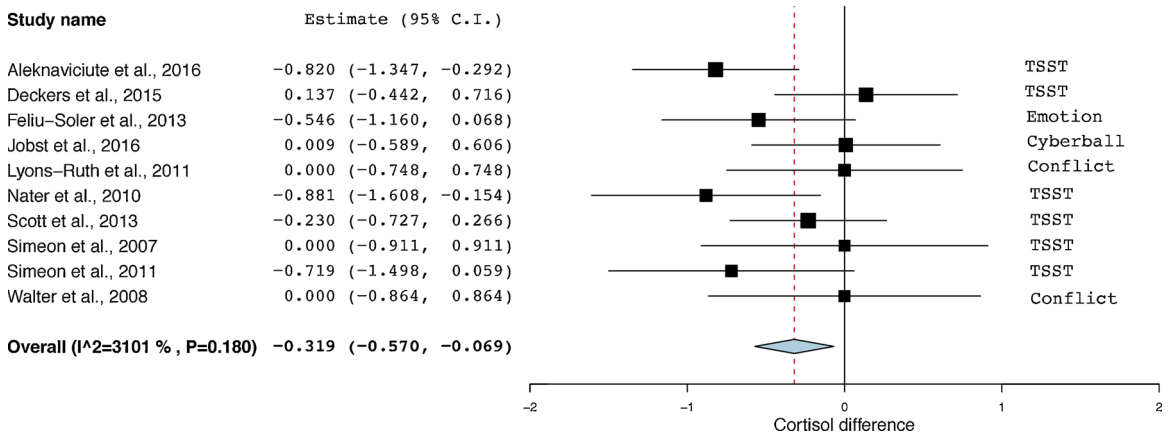

Fig. 9. Forest plot comparing cortisol values during psychosocial stress in BPD patients and HC. Details on the respective psychosocial challenge are noted on the right side of the figure. TSST = Trier Social Stress Test; Emotion = Emotion Induction procedure; Conflict = Conflict Discussion; Cyberball = Cyberball paradigm.

p = . 192; I^2 = 41%). None of the studies compared BPD and MDD patients based on psychosocial stress tests.

3.5.9. Meta-regressions comparing cortisol assessments based on psychosocial challenges

Meta-regressions are reported for studies comparing BPD to HC based on cortisol assessments during psychosocial challenges (all k = 10). Study quality had a significant impact on the main effect (β = -.095, *95% CI* [-0.18, -0.01], *SE* = .04, p = .026). Differences in cortisol were larger (i.e., relatively more blunted response in BPD) in high-quality studies as shown in Fig. S8 (Supplement 1). Removing the leverage point further increased the estimate reported (β = -.176, *95% CI* [-0.31, -0.04], *SE* = .07, p = .009). Besides, studies using unmedicated BPD patients were characterized by larger differences in cortisol, β = -.570, *95% CI* [-0.99, -0.14], *SE* = .22, p = .009. Neither age (β= -.013, *95% CI* [-0.06, 0.03], *SE* = .02, p = .573), nor sex (β = 0.000, *95% CI* [-0.01, 0.01], *SE* = .01, p = .982), nor matched participant characteristics (β = -.053, *95% CI* [-0.17, 0.07], *SE* = .06, p = .390), nor sampling material (β = .141, *95% CI*[-0.40, 0.68], *SE* = .28, p = .607), nor assessment time (β = .141, *95% CI* [-0.40, 0.68], *SE* = .28, p = .607), nor type of psychosocial challenge (all $p \geq$ .323; Table 2) were significant covariates. No differences in cortisol emerged when different psychosocial challenges were used as reference groups for the respective meta-regression (data not shown).

3.5.10. Risk of bias across studies focusing on cortisol assessments based on psychosocial challenges

For studies investigating stress responses during psychosocial challenges in BPD patients and HC, no publication bias was present based on visual inspection or Egger's test (intercept = 0.65, *95% CI* [-4.44, 5.74], p = . 388, k = 10). As shown in Fig. S9 (Supplement 1), the trim and fill procedure did not impute any studies, yielding an estimate similar to the initial ES (Hedges' g = -0.32, *95% CI* [-0.56, -0.07]). In contrast, publication bias was indicated for studies examining recovery from psychosocial challenges in BPD patients and HC (Egger's test: intercept = 2.97, *95% CI* [-0.72, 6.66], p = . 049, k = 9). As shown in Fig. S10 (Supplement 1), the trim and fill procedure imputed two studies for the comparison of recovery from psychosocial challenges, yielding a still significant ES of Hedges' g = -0.37, *95% CI* [-0.57, -0.17].

4. Discussion

The current set of meta-analyses examined HPA axis functioning in BPD patients as compared to healthy controls and patients with Major Depressive Disorder or other Personality Disorders. Based on the included studies, HPA axis functioning was examined with singular and continuous cortisol assessments as well as cortisol responses to pharmacological or psychosocial challenges. Our main findings are that BPD patients displayed augmented continuous cortisol output but blunted cortisol responses to psychosocial challenges. Comparing singular cortisol assessments did not indicate abnormal HPA axis functioning. Besides, HPA axis suppression due to pharmacological challenges did not impact BPD patients differently than healthy or clinical controls.

Most importantly, HPA axis functioning in BPD patients was blunted in response to psychosocial stress and also during recovery from

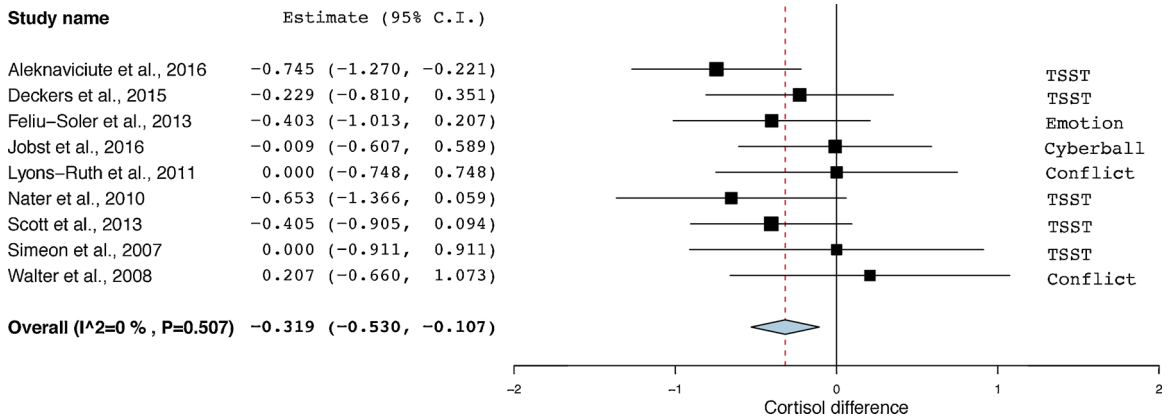

Fig. 10. Forest plot comparing cortisol values after psychosocial stress in BPD patients and HC. Details on the respective psychosocial challenge are noted on the right side of the figure. TSST = Trier Social Stress Test; Emotion = Emotion Induction procedure; Conflict = Conflict Discussion; Cyberball = Cyberball paradigm.

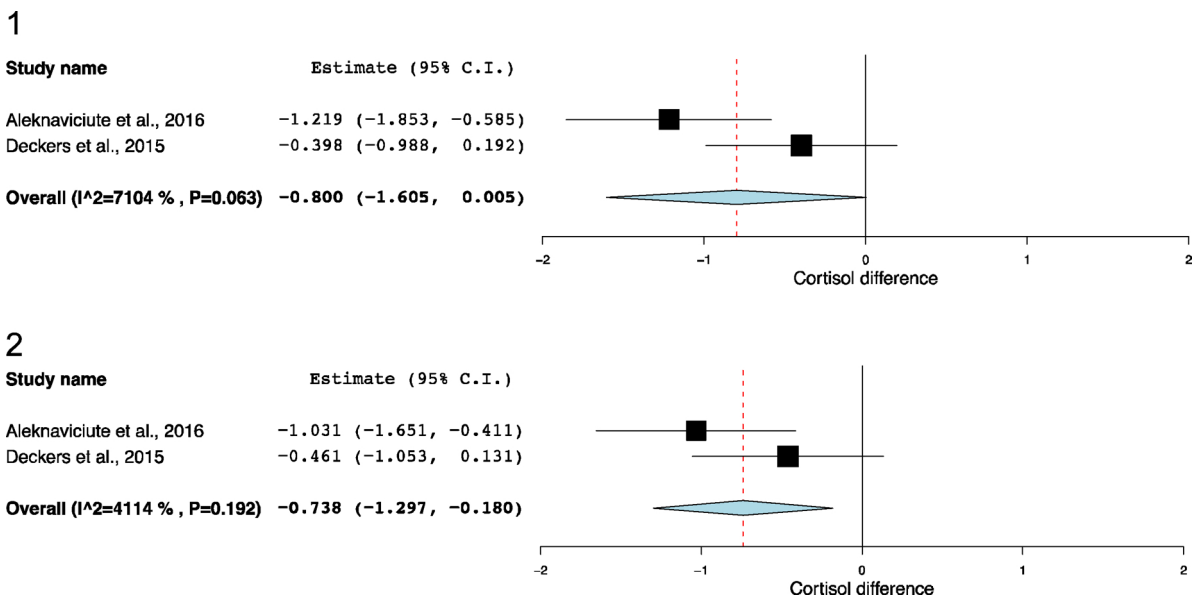

Fig. 11. Forest plots comparing cortisol values during psychosocial stress (11.1) and after psychosocial stress (11.2) in BPD patients and patients with other patients with other Personality Disorders. Both studies applied the TSST.

Table 2
Meta-regression to examine how different types of psychosocial challenges are related to cortisol outcomes when comparing BPD patients to HC.

Variable	*k*	*β*	*95% CI*	*SE*	*p*
Intercept		.380	[−0.83, 0.07]	.23	.094
Conflict Discussion	2				
Cyberball	1	.380	[−0.51, 1.27]	.46	.404
Emotion Induction	1	−.389	−0.38, 1.16]	.39	.323
Trier Social Stress Test	6	−.029	−0.56, 0.50]	.27	.915

psychosocial stress. Interestingly, blunted cortisol responses not only became apparent when considering healthy individuals as comparison but also when comparing BPD patients to patients presenting with other Personality Disorders. This likely indicates that the attenuated neuroendocrinological stress response to psychosocial encounters is a BPD-specific phenomenon. Further, our findings correspond to research showing that BPD patients are often characterized by inadequate psychosocial functioning (Pagano et al., 2004). On a neurobiological level, these findings potentially also suggest that BPD patients display decreased adrenal responsiveness to endogenous ACTH. Thereby, blunted cortisol responses to psychosocial stress imply a potential pharmacological target in the treatment of BPD warranting further study. However, prior research also suggested that aberrant neuroendocrinological responses to psychosocial stress may result from childhood adversity, which likely causes an attenuated cortisol response to future stress (Carpenter et al., 2011). Hence, childhood adversity may lead to a so-called HPA axis 'burn-out' phenomenon, in which hypercortisolism during early neurodevelopment modifies later HPA axis functioning. Correspondingly, Danese and McEwen (2012, p.32) hypothesized that *"the blunted cortisol responses to psychosocial stressors … could be due to a compensatory down-regulation of the central negative feedback mechanism regulating the HPA axis"*. Support for this hypothesis has been provided by an earlier study of our group, where we could show that female adolescents engaging in Nonsuicidal Self-Injury (NSSI) display attenuated cortisol responses to psychosocial stress (Kaess et al., 2012). Since NSSI is a characteristic early marker in the course of BPD (Ferrara et al., 2012) and existing research suggests that childhood adversity may cause endocrinological alterations (Koss and Gunnar, 2017), these findings likely indicate that hypocortisolism towards psychosocial stress characterizes BPD patients in the long term. However, as only a fraction of the included studies assessed or reported childhood trauma, future research has to determine the causal link between adverse childhood experiences and HPA axis functioning in patients with BPD.

Focusing on origins and development of altered HPA axis functioning in BPD patients seems further important to increase our understanding of behaviors associated with stressful situations, such as anger, suicidality and impulsivity. Accordingly, it seems likely that neuroendocrine responses to stress are also identifiable in close interpersonal relationships and therapeutic encounters. As it has been proposed that acute stress-related symptoms may be more modifiable than chronic symptoms (Bourvis et al., 2017)[18], these behaviors likely constitute important treatment targets, which could be operationalized based on HPA axis assessments in future research. However, we recommend that future studies combine such assessments with instruments assessing subjective stress experiences when implementing HPA axis assessments as biological markers of treatment outcome. If blunted cortisol secretion is indeed associated with increased stress perception in patients with BPD, then cortisol reactivity might be suitable to examine psychosocial stress within therapeutic relationships, as past research demonstrated associations between cortisol reactivity and treatment outcome (Fischer and Cleare, 2017; van de Wiel et al., 2004). Such a line of research appears particularly promising since cortisol responses to therapeutic encounters provide a relatively unbiased, yet dynamic marker of treatment effectiveness when measured repeatedly and under controlled conditions (Miller et al., 2010).

Moreover, we were able to show that continuous cortisol levels are elevated in BPD patients. Increased continuous cortisol secretion likely indicates that patients with BPD experience more daily hassles and inner tension during the day (Rausch et al., 2015) or that they feel generally more vigilant towards potentially threatening events (Nater et al., 2010; Smyth et al., 1998). Even though it has been speculated that the anticipation of upcoming demands impinges on continuous cortisol production (Fries et al., 2009), it remains to be investigated how elevated continuous cortisol corresponds to blunted cortisol responses following psychosocial stress. If elevated continuous cortisol is related to blunted cortisol responsivity following psychosocial stress, then a therapeutic target could be to help patients reduce continuous

[18] chronic symptoms encompass feelings of emptiness, fear of abandonment, and instable relationship patterns.

cortisol levels, for instance by reducing stress as well as general negative mood, and finding safety in their daily life. Potentially, long-term reductions of circulating cortisol would also improve negative feedback functioning relevant for the stress response, which might enable BPD patients to display more adaptive responses to momentary stressors. Either way, this combined finding suggests a complex picture of HPA axis dysregulation specific to BPD, which can be characterized by higher resting arousal and a dysregulated reactivity to psychosocial stress. Correspondingly, it needs to be mentioned that the finding of elevated continuous cortisol seemingly contradicts unaltered singular cortisol assessments. In this context, the critical reader should keep in mind that especially singular cortisol assessments were assessed in a heterogeneous manner, which may have biased the meta-analytic findings. For instance, we cannot fully outrule the possibility that additional factors, such as exercise, smoking, or food prior to participation, influenced the comparisons systematically in cases where these factors were not reported in primary studies. Moreover, it should be kept in mind that singular cortisol assessments are of limited explanatory value given their susceptibility to nonspecific arousal and frequent neglect of crucial influences such as daytime (Kaess et al., 2013). Given that heterogeneity was particularly high for the comparison of singular cortisol assessments between BPD patients and HC and taking into account that most other comparisons were based on a small number of studies, firmer conclusions can be drawn once a larger number of sensitive dynamic tests has been carried out to evaluate HPA axis functioning in BPD patients. In this context, we recommend to address HPA axis impairment within ecologically valid contexts, for instance based on assessments using the cortisol awakening response (CAR). CAR measures can be considered particularly sensitive assessments of cortisol production over a limited period of time. CAR measures are further important to examine the diurnal rhythm of the HPA axis in BPD patients. Since only two studies (Lieb et al., 2004; Rausch et al., 2015) assessed CAR in adult BPD patients up to now, we did not meta-analyze this assessment type. However, as CAR assessments are particularly reliable trait measures of basal HPA axis activity (Hellhammer et al., 2007), increased focus on these repeated cortisol assessments is warranted.

Lastly, there were no group differences for cortisol responses to pharmacological challenges and these meta-analyses were associated with variable heterogeneity depending on the control group. Even though earlier research suggested that pharmacological challenges are of diagnostic value for different psychopathologies (Bourvis et al., 2017), our findings suggest that challenges based on dexamethasone do not distinguish BPD patients from other groups. Unfortunately, assessing potential dose-response relationships among dexamethasone and cortisol suppression based on meta-regressions was impossible due to the small number of available comparisons. Based on our findings, however, it seems unlikely that pharmacological challenges are sensitive enough to measure feedback inhibition in patients with BPD, especially when considering that these challenges were originally developed to diagnose endocrine disorders such as Cushing's disease (de Kloet et al., 2006; Kirschbaum and Hellhammer, 1994). Nevertheless, it may be worthwhile to pay attention to more recent pharmacological challenges such as challenges based on hydrocortisone administration. For instance, Wingenfeld and Wolf (2015) recently showed that hydrocortisone administration enhances cognitive functioning in patients with BPD. Consequently, differential effects of cortisol enhancements and diminutions in BPD patients may be addressed in future studies.

The results of the current set of meta-analyses should be interpreted in light of its limitations and strengths. First, it should be noted that this meta-analytic research primarily aimed at providing a comprehensive overview of HPA axis functioning under certain conditions by comparing cortisol levels in BPD patients to those of HC and CC. However, due to the broad spectrum of individual studies, clusters of studies included within single comparisons were potentially rather heterogeneous. While we clustered studies according to experimental groups and comparable outcomes, it needs to be stressed that different study designs were integrated within the same meta-analytic comparison. Despite the fact that potential confounders were examined extensively based on meta-regressions and risk of bias assessments, more careful research on HPA axis functioning in BPD patients is needed to validate and replicate our current findings. In this context, it needs to be emphasized that meta-regressions could only be carried out for a limited number of cortisol assessments and were based on group-level data instead of individual characteristics of the participants. Although the current findings indicate that attention should primarily be paid to quality-related aspects, it seems worthwhile to investigate individual patient-level data on HPA axis functioning in BPD patients. Also, we recommend that future studies focus increasingly on different CC groups as comparison or designs different from singular cortisol assessments or psychosocial challenges. Second, only a few studies reported on symptom severity or comorbid disorders in patients with BPD. Consequently, neither the impact of symptom severity nor comorbidities could be investigated systematically. The respective meta-analyses would have been meaningful to further address the specificity of altered HPA axis functioning in patients with BPD. For example, more than a third of the included studies did not mention PTSD comorbidity despite its high prevalence in BPD and its well-known impact on the HPA axis (Morris et al., 2012). Similarly, only a fraction of the included studies reported explicitly on childhood adversity. Additionally, it was frequently not disclosed whether current or lifetime comorbid disorders were assessed, albeit their differential impact on HPA axis activity (Dickerson and Kemeny, 2004). Despite the findings that emerged from the present series of meta-analyses, investigating these critical aspects would have been important to address confounding effects alongside BPD pathology. We recommend that future studies incorporate and report on structured assessments of symptom severity and comorbid diagnoses, enabling their investigation in systematic reviews and meta-analyses. Third, while the blunted cortisol response to psychosocial stress can be considered a key feature of BPD patients, no direct inferences on subjective stress levels of BPD patients should be drawn based on the current set of meta-analyses. Previous studies operationalized stress perception primarily based on pain sensitivity or exposure to psychosocial stress (Bourvis et al., 2017), yet an adequate operationalization of subjective stress perception and its relationship to HPA axis assessments remains a matter of debate. Again, as only a minority of studies assessed subjective stress perception during HPA axis assessments, future studies should combine HPA axis assessments with subjective stress measures. Lastly, in spite of our aim to comprehensively examine HPA axis functioning, only studies investigating cortisol could be included in the current set of meta-analyses. Even though cortisol is a frequently used and highly relevant endocrinological marker, it should be kept in mind that CRH and ACTH also contribute to HPA axis functioning. An improved understanding of these markers is required when examining HPA axis functioning in BPD patients.

The merits of this investigation primarily rest on its methodological rigor in terms of procedures related to search strategies, data collection processes, and subsequent statistical analyses. Hence, it was aimed at overcoming the selective availability of data by searching multiple databases including databases containing grey literature (Hopewell et al., 2007). The large number of meta-analytic comparisons based on several methods and comparison groups further allowed for a nuanced description of HPA axis functioning in BPD patients. This differentiation of HPA axis functioning in BPD patients could additionally be sharpened through a series of meta-regressions where characteristics inherent to this patient group and aspects appertaining to the respective study designs were systematically examined. Further, this differentiation was facilitated by a detailed quality assessment, which has been designed to assess risk of bias within individual studies for the current set of meta-analyses. Risk of bias across studies was examined based on funnel plots and corresponding statistical analyses in order to measure

aspects such as publication bias or selective reporting within studies. Thereby, the current set of meta-analyses helped defining the necessary framework conditions to thoroughly understand the biological underpinnings of abnormal stress sensitivity in BPD patients.

5. Conclusion

Results of this meta-analytic review revealed altered HPA axis functioning in BPD patients. Remarkably, continuous cortisol output was augmented while cortisol during and after exposure to psychosocial stress was attenuated. Meta-regressions revealed that high-quality studies were associated with smaller differences between BPD patients and clinical or healthy controls than studies of lower quality. To better understand the linkage between BPD symptoms and HPA axis development, future studies should focus increasingly on repeated long-term cortisol assessments as well as cortisol reactivity to different experimental conditions. Moreover, research needs to implement dynamic measures of the biological stress response in therapeutic environments to scrutinize if cortisol assessments constitute valid markers of treatment effectiveness. Eventually, such investigations may allow for diagnostic and therapeutic differentiation of BPD patients based on their endocrinological profiles.

Conflict of interest

None.

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Appendix A

Full electronic search strategy including hits per search term as used for PsycINFO (Ovid) on April 17, 2017.

1 Borderline personality disorder.mp. [mp = title, abstract, heading word, table of contents, key concept, original title, tests & measures] *(8926)*
2 borderline patient*.mp. [mp = title, abstract, heading word, table of contents, key concept, original title, tests & measures] *(2046)*
3 emotionally unstable personality disorder.mp. [mp = title, abstract, heading word, table of contents, key concept, original title, tests & measures] *(39)*
4 1 or 2 or 3 *(*10134*)*
5 dexamethasone.mp. [mp = title, abstract, heading word, table of contents, key concept, original title, tests & measures] *(3561)*
6 hydrocortison*.mp. [mp = title, abstract, heading word, table of contents, key concept, original title, tests & measures] *(7564)*
7 cortisol.mp. [mp = title, abstract, heading word, table of contents, key concept, original title, tests & measures] *(13500)*
8 HPA.mp. [mp = title, abstract, heading word, table of contents, key concept, original title, tests & measures] *(5680)*
9 hypothalamic pituitary adrenal axis.mp. [mp = title, abstract, heading word, table of contents, key concept, original title, tests & measures] *(5553)*
10 CRH.mp. [mp = title, abstract, heading word, table of contents, key concept, original title, tests & measures] *(1429)*
11 corticotropin releasing hormone.mp. [mp = title, abstract, heading word, table of contents, key concept, original title, tests & measures] *(1401)*
12 hormone*.mp. [mp = title, abstract, heading word, table of contents, key concept, original title, tests & measures] *(33222)*
13 feedback regulation.mp. [mp = title, abstract, heading word, table of contents, key concept, original title, tests & measures] *(236)*
14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 *(48209)*
15 4 and 14 *(136)*
16 limit 15 to (adulthood < 18 + years > and “300 adulthood < age 18 yrs and older > ” and human and yr = ”1980-Current”) *(81)*

Appendix B

See Table B1.

Table B1
Items of the adjusted quality assessment used to gauge the risk of bias within studies.

Appropriate Selection of Participants		
1. Has BPD been reliably assessed and validated?		
	2 points	Based on a (semi-structured) clinical interview including check on inter-rater reliability (sufficient Cohen's kappa value)
	1 point	Based on a (semi-structured) clinical interview
	0 points	Self-report or not clearly stated
2. How were control participants recruited?		
	2 points	From the general population
	1 point	From a selected population, such as hospital staff or students
	0 points	Not clearly stated
3. Is the population defined with in- and exclusion criteria?		
	2 points	3 criteria stated
	1 point	1-2 criteria stated
	0 points	No criteria stated or not clearly stated
4. Did the authors explicitly exclude individuals with endocrine disorders?		
	2 points	Individuals with endocrine disorders were explicitly excluded
	1 point	Individuals with endocrine disorders were implicitly excluded (e.g., only physically healthy individuals included)
	0 points	Endocrine disorders were not mentioned at all
Appropriate Quantification of HPA Axis Function		
5. Is the assessor of the HPA axis blind for the disorder status of the participants?		
	2 points	Yes
	0 points	Not clearly stated
6. Are the methods for the assessment of HPA axis functioning clearly stated? *Relevant aspects: time of day, behavior shortly prior to measurement, storage conditions, type of assay performed, repeated measurements, assessing compliance*		
	2 points	5-6 criteria stated
	1 point	3-4 criteria stated
	0 points	0-2 criteria stated
7. Is the outcome HPA axis measurement clearly described and presented?		
	2 points	Central tendency and measures of dispersion are stated in appropriate units
	1 point	Only central tendency but no measures of dispersion are stated in appropriate units
	0 points	Outcome is not clearly stated
Control for Confounding		
8. Are potential confounders assessed? *Relevant aspects: age, sex, body mass index, smoking, depression/PTSD, medication, physical exercise, menstrual cycle/menopausal status*		
	2 points	6-8 criteria stated
	1 point	3-5 criteria stated
	0 points	0-2 criteria stated
9. Are the analyses adjusted for potential confounders? *Relevant aspects: age, sex, body mass index, smoking, depression/PTSD, medication, physical exercise, menstrual cycle/menopausal status*		
	2 points	Analyses were adjusted for 6-8 criteria
	1 point	Analyses were adjusted for 3-5 criteria
	0 points	Analyses were adjusted for 0-2 criteria
Additional Questions: Experimental Designs		
10. Did the authors check if the experimental manipulation was successful?		
	2 points	A manipulation check indicated that the manipulation was successful
	1 point	A manipulation check has been included
	0 points	No manipulation check has been included
11. Did the authors check if the psychosocial stress task indeed induced stress?		
	2 points	The authors examined if subjective stress changed over time due to the stress tasks (e.g., with a visual analogue scale)
	1 point	The authors examined if aspects related to stress changed over time due to the stressor task (e.g., mood or aggression)
	0 points	The authors did not examine if subjective stress levels changed over time due to the stressor task

Note. The last two questions were only posed for studies using pharmacological or psychosocial challenges.

Appendix C

See Table C1.

Table C1
Quality ratings for the individual studies that were included in three different meta-analyses.

(1) Singular and Continuous Measurements

Study	Selection of Participants					HPA Axis Measure				Control for Confounding			Experimental Design			Score	
Item	1	2	3	4	Score	5	6	7	Score	8	9	Score	10	11	Score	Relative	Absolute
Bromundt et al., 2013	1	1	1	1	**4**	0	1	2	**3**	1	0	**1**	NA	NA	NA	**8**	**8**
Carrasco et al., 2003	1	1	1	0	**3**	0	1	1	**2**	0	0	**0**	NA	NA	NA	**5**	**5**
Carvalho Fernando et al., 2013	1	2	2	2	**7**	2	2	2	**6**	2	1	**3**	NA	NA	NA	**16**	**16**
Garbutt et al., 1983	1	0	2	2	**5**	0	2	2	**4**	1	1	**2**	NA	NA	NA	**11**	**11**
Hollander et al., 1994	1	1	1	0	**3**	2	1	1	**4**	1	0	**1**	NA	NA	NA	**8**	**8**
Jogems-Kosterman et al., 2007	1	1	1	0	**3**	0	1	2	**3**	2	0	**2**	NA	NA	NA	**8**	**8**
Kahl et al., 2005a	1	0	1	1	**3**	0	1	2	**3**	1	0	**1**	NA	NA	NA	**7**	**7**
Kahl et al., 2005b	1	1	2	1	**5**	0	1	2	**3**	1	0	**1**	NA	NA	NA	**9**	**9**
Kahl et al., 2006a	1	0	2	1	**4**	0	1	2	**3**	1	1	**2**	NA	NA	NA	**9**	**9**
Kahl et al., 2006b	1	0	2	1	**2**	0	2	2	**3**	2	1	**3**	NA	NA	NA	**11**	**11**
Martial et al., 1997	1	0	2	1	**4**	0	2	2	**4**	2	1	**3**	NA	NA	NA	**11**	**11**
Paris et al., 2004	2	2	1	0	**5**	0	1	2	**3**	1	0	**1**	NA	NA	NA	**9**	**9**
Rausch et al., 2015	1	2	2	1	**6**	0	2	2	**4**	2	2	**4**	NA	NA	NA	**14**	**14**
Rinne et al., 2000	1	1	1	1	**4**	0	2	2	**4**	1	0	**1**	NA	NA	NA	**9**	**9**
Roepke et al., 2010	1	0	2	0	**3**	0	2	2	**4**	2	1	**3**	NA	NA	NA	**10**	**10**
Sinai et al., 2015	1	0	1	2	**4**	0	0	2	**2**	1	0	**1**	NA	NA	NA	**7**	**7**
Steiger et al., 2001	2	1	2	0	**5**	0	2	2	**4**	2	1	**3**	NA	NA	NA	**12**	**12**
Steinberg et al., 1997	2	2	1	2	**7**	0	2	1	**3**	1	1	**2**	NA	NA	NA	**12**	**12**
Wingenfeld et al., 2007	1	0	2	1	**4**	0	1	2	**3**	1	1	**2**	NA	NA	NA	**9**	**9**

(2) Pharmacological Challenges

Study	Selection of Participants					HPA Axis Measure				Control for Confounding			Experimental Design			Score	
Item	1	2	3	4	Score	5	6	7	Score	8	9	Score	10	11	Score	Relative	Absolute
Beeber et al., 1984	1	1	2	2	**6**	0	1	0	**1**	0	0	**0**	0	NA	**0**	**7**	**7**
Carrasco et al., 2007	2	1	2	2	**7**	0	1	2	**3**	1	1	**2**	0	NA	**0**	**12**	**12**
De la Fuente et al., 2002a	1	1	2	1	**5**	0	1	2	**3**	1	1	**2**	1	NA	**1**	**10**	**11**
Carvalho Fernando et al., 2012	1	2	2	2	**7**	0	2	2	**4**	2	1	**3**	0	NA	**0**	**14**	**14**
Kontaxakis et al., 1987	1	1	2	2	**6**	2	1	1	**4**	1	0	**1**	0	NA	**0**	**11**	**11**
Lee et al., 2012	2	2	1	2	**7**	0	2	2	**4**	2	1	**3**	1	NA	**1**	**14**	**15**
Lieb et al., 2004	1	1	2	0	**4**	0	2	2	**4**	2	2	**4**	0	NA	**0**	**12**	**12**

(3) Psychosocial Challenges

Study	Selection of Participants					HPA Axis Measure				Control for Confounding			Experimental Design			Score	
Item	1	2	3	4	Score	5	6	7	Score	8	9	Score	10	11	Score	Relative	Absolute
Aleknaviciute et al., 2016	1	2	2	2	**7**	0	2	2	**4**	2	2	**4**	2	1	**3**	**15**	**18**
Deckers et al., 2015	1	1	2	2	**6**	0	2	2	**4**	2	1	**3**	0	2	**2**	**13**	**15**
Feliu-Soler et al., 2013	2	1	2	1	**6**	0	2	2	**4**	2	2	**4**	2	2	**4**	**14**	**18**
Inoue et al., 2015	1	2	2	1	**6**	0	2	2	**4**	2	2	**4**	1	0	**1**	**14**	**15**
Jobst et al., 2016	1	2	2	0	**5**	0	2	2	**4**	1	1	**2**	1	2	**3**	**11**	**14**
Lyons-Ruth et al., 2011	1	2	2	0	**5**	0	2	2	**4**	1	1	**2**	2	2	**4**	**11**	**15**
Nater et al., 2010	2	2	2	1	**7**	0	2	2	**4**	2	2	**4**	2	2	**4**	**15**	**19**
Scott et al., 2013	2	1	2	2	**7**	0	2	2	**4**	2	1	**2**	2	2	**4**	**14**	**18**
Simeon et al., 2007	1	0	2	1	**4**	0	2	2	**4**	1	1	**2**	2	2	**4**	**10**	**14**
Simeon et al., 2011	1	0	2	1	**4**	2	2	2	**6**	2	1	**3**	2	1	**3**	**13**	**16**
Walter et al., 2008	1	0	1	0	**2**	0	1	2	**3**	0	0	**0**	0	0	**0**	**5**	**5**

Note. Relative scores include the first nine items; absolute scores include the remaining two items specific to experimental designs. The full items are reported in Appendix B.

Appendix D. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2018.11.008.

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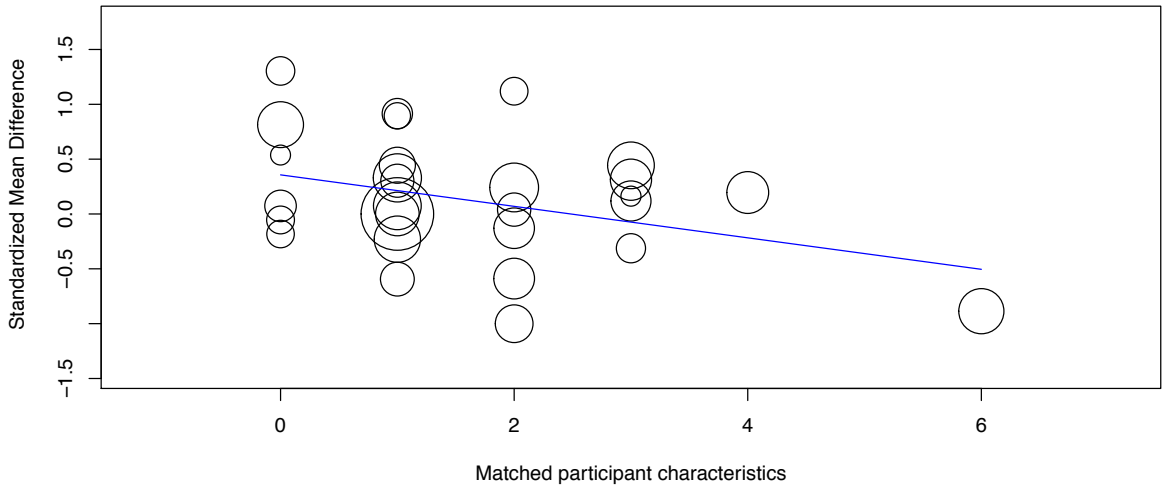

Fig.S1. Meta-regression on differences in reported effect sizes for singular cortisol assessments by matched participant characteristics in BPD patients and healthy controls.

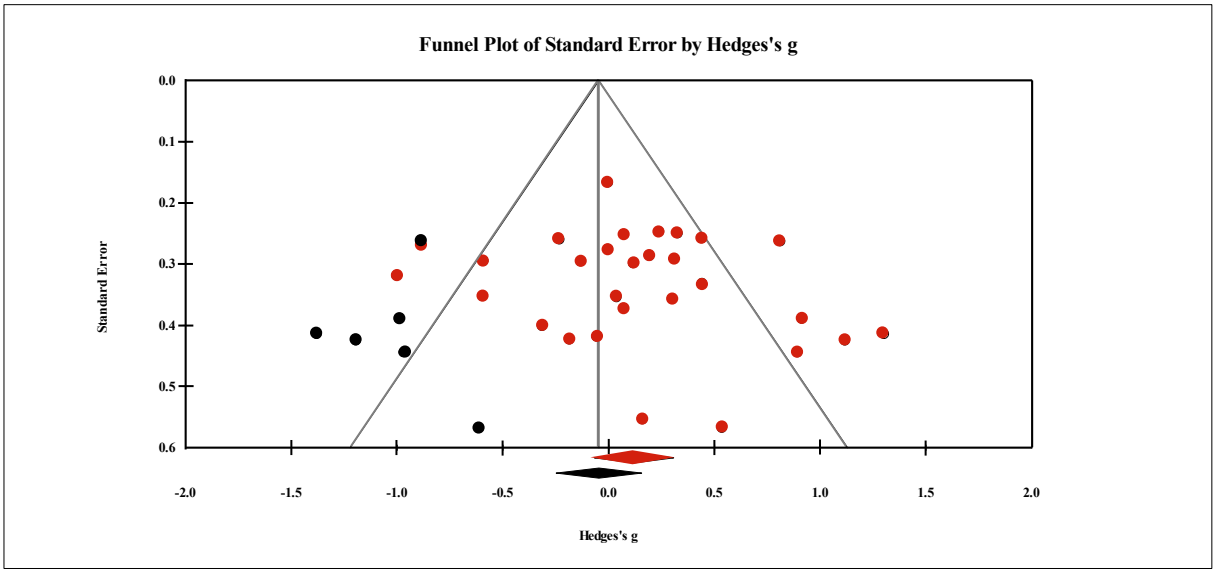

Fig.S2. Funnel plot for the comparison of singular cortisol assessments in BPD patients and healthy controls based on the relationship between Hedges' *g* and standard errors of the corresponding studies using pseudo 95% confidence limits. Red circles indicate observed studies; black circles indicate imputed studies.

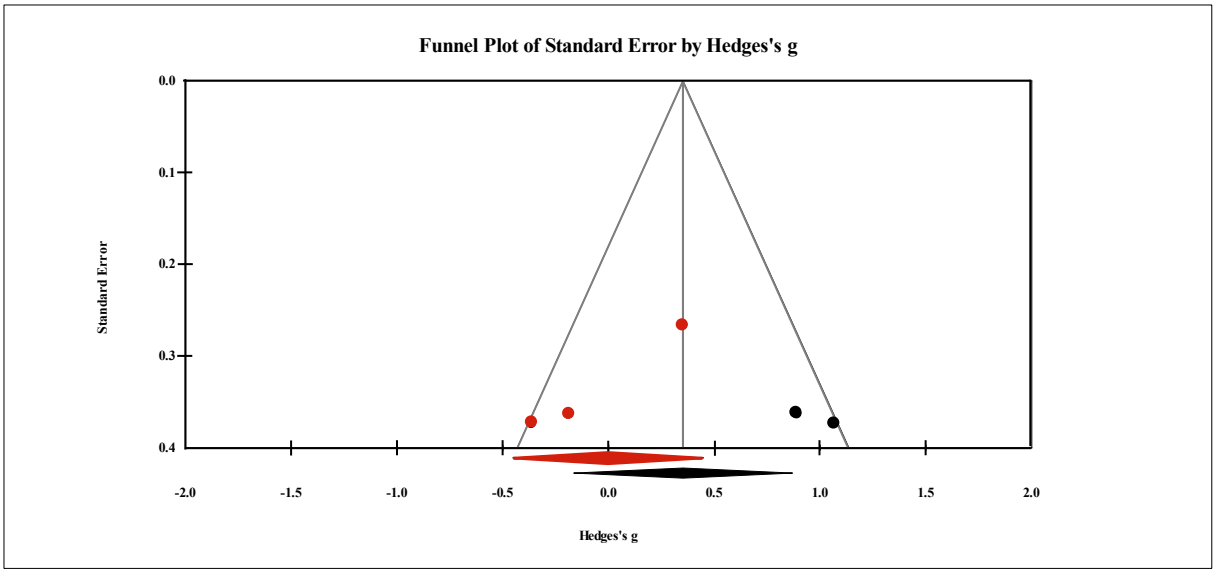

Fig.S3. Funnel plot for the comparison of single cortisol assessments in BPD and MDD patients based on the relationship between Hedges' *g* and standard errors of the corresponding studies using pseudo 95% confidence limits. Red circles indicate observed studies; black circles indicate imputed studies.

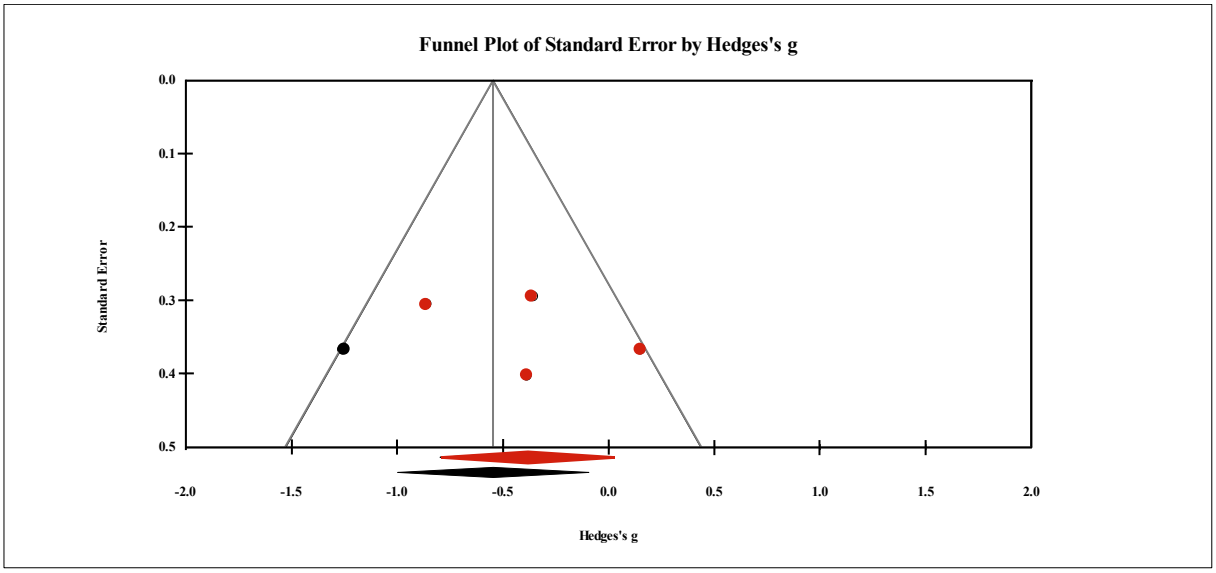

Fig.S4. Funnel plot for the comparison of single cortisol assessments in BPD patients and patients suffering from other personality disorders based on the relationship between Hedges' *g* and standard errors of the corresponding studies using pseudo 95% confidence limits. Red circles indicate observed studies; black circles indicate imputed studies.

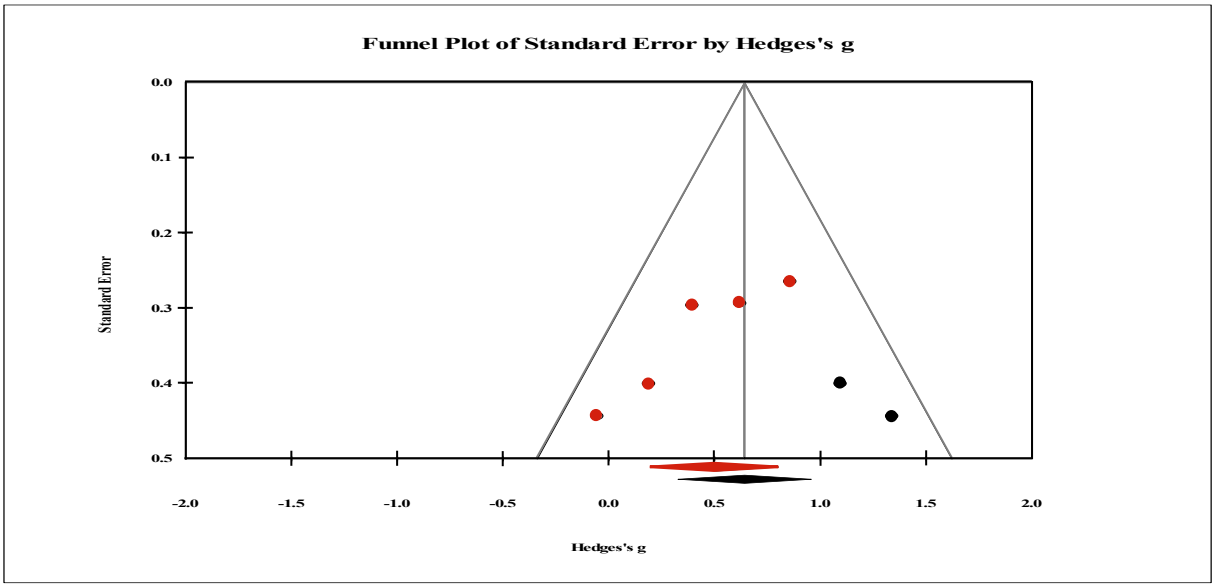

Fig.S5. Funnel plot for the comparison of continuous cortisol values in BPD patients and healthy controls based on the relationship between Hedges' *g* and standard errors of the corresponding studies using pseudo 95% confidence limits. Red circles indicate observed studies; black circles indicate imputed studies.

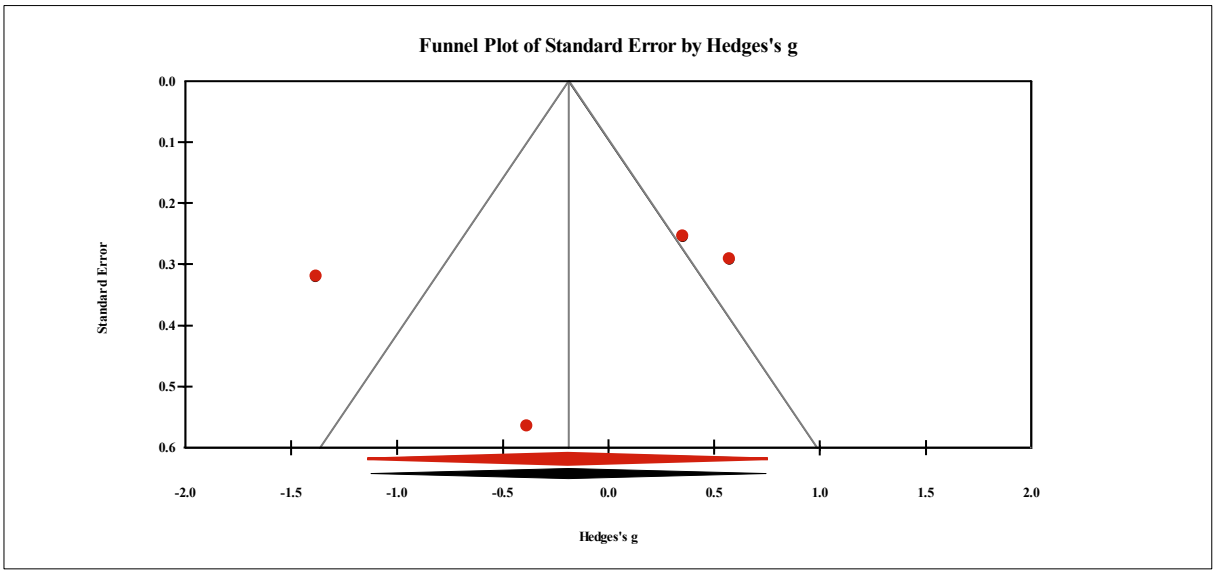

Fig.S6. Funnel plot for the comparison of pharmacological challenges in BPD patients and healthy controls based on the relationship between Hedges' *g* and standard errors of the corresponding studies using pseudo 95% confidence limits. Red circles indicate observed studies.

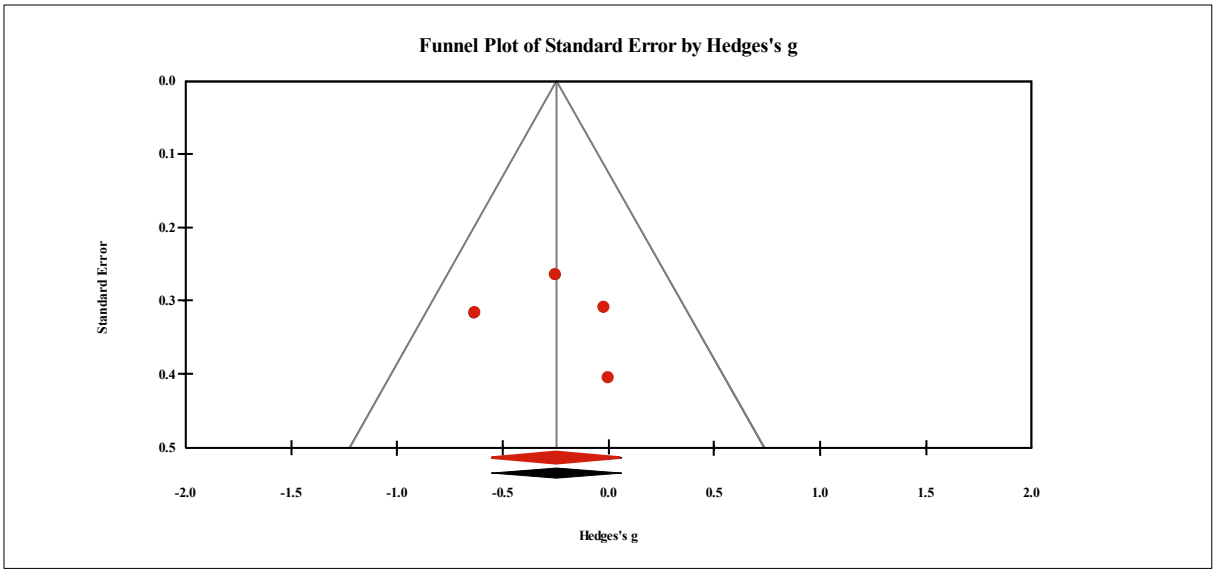

Fig.S7. Funnel plot for the comparison of pharmacological challenges in BPD patients and MDD patients based on the relationship between Hedges' *g* and standard errors of the corresponding studies using pseudo 95% confidence limits. Red circles indicate observed studies.

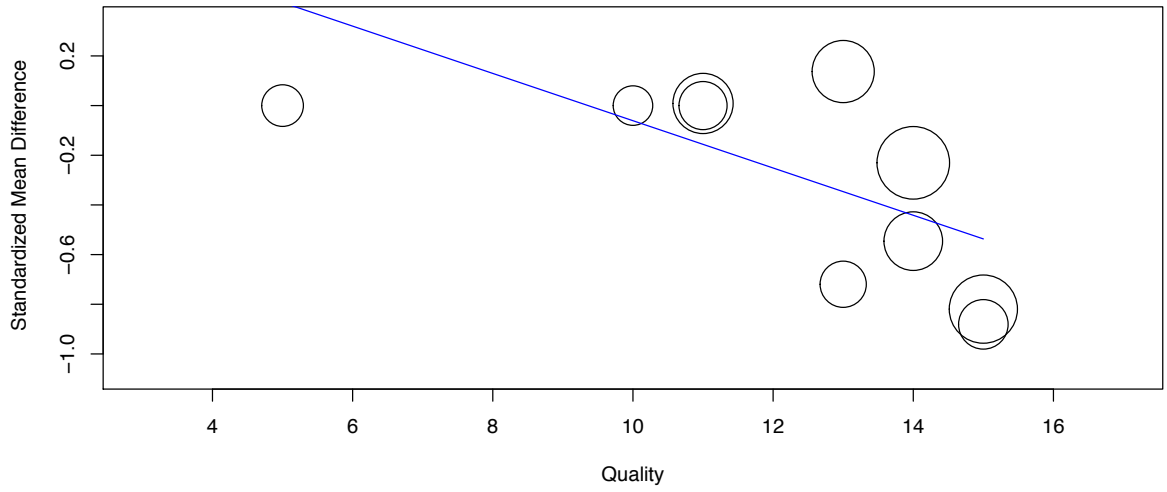

Fig.S8. Meta-regression on differences in reported effect sizes during psychosocial challenges by study quality in BPD patients and healthy controls.

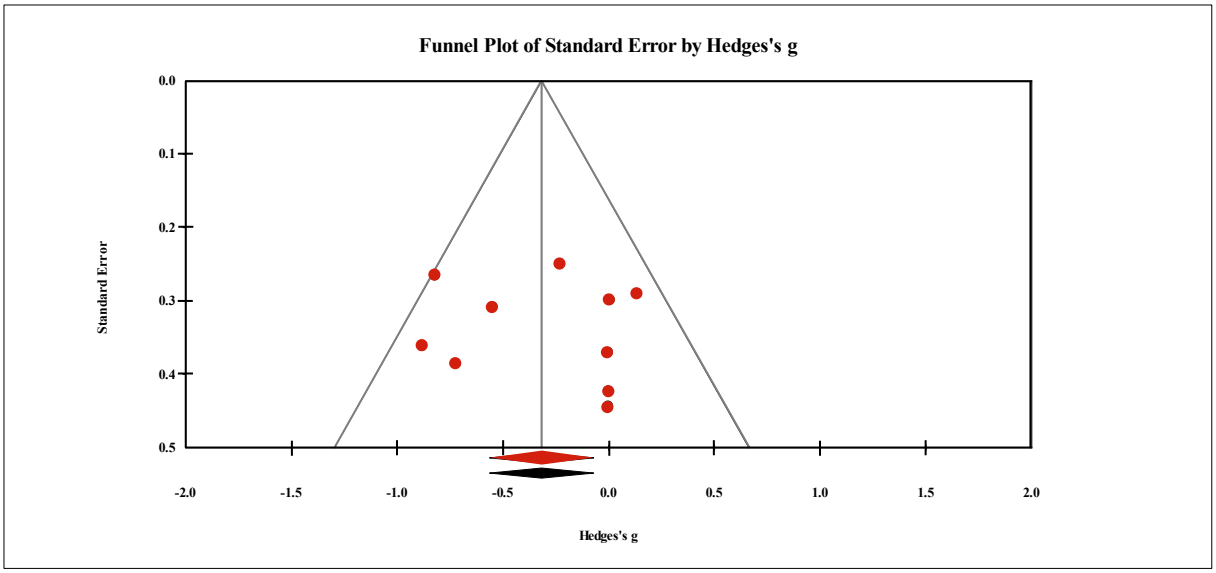

Fig.S9. Funnel plot for the comparison of cortisol responses during psychosocial stress in BPD patients and healthy controls based on the relationship between Hedges' *g* and standard errors of the corresponding studies using pseudo 95% confidence limits. Red circles indicate observed studies.

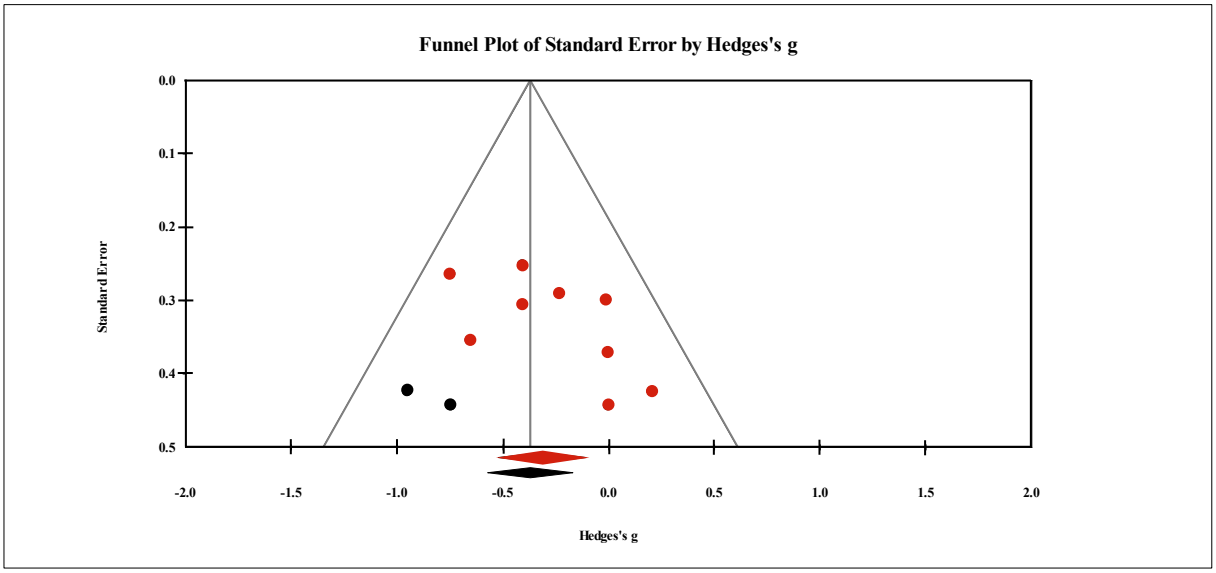

Fig.S10. Funnel plot for the comparison of cortisol responses after psychosocial stress in BPD patients and healthy controls based on the relationship between Hedges' *g* and standard errors of the corresponding studies using pseudo 95% confidence limits. Red circles indicate observed studies; black circles indicate imputed studies.

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PSYCHIATRY AND PRECLINICAL PSYCHIATRIC STUDIES - ORIGINAL ARTICLE

Associations between age and cortisol awakening response in patients with borderline personality disorder

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Abstract
Patients with borderline personality disorder (BPD) often display increased stress vulnerability, which may be linked to altered hypothalamus–pituitary–adrenal (HPA) axis functioning. Corresponding deviations of the cortisol awakening response (CAR) are presumed to mirror maladaptive neuroendocrine processes, which may explain why CARs are increased compared to healthy controls (HC). Prior research speculated that these alterations may be caused by early life stress and/or chronic stress related to the ongoing burden of the disorder. Yet, it remains to be investigated how BPD influences CAR in the course of development. Therefore, the current study examined CAR in female adolescents and adults with BPD compared to HC with a particular focus on associations with age. These potential associations were especially focused, as it was hypothesized that the CAR would be even more elevated (i.e., higher) in older individuals with BPD. CAR was assessed in 54 female individuals with BPD (aged 15–40 years) and 54 sex-, age-, and intelligence-matched HC (aged 15–48 years). Group differences were investigated and analyses of covariance using age as continuous predictor were performed to analyze potential developmental associations with CAR alongside BPD-specific effects. Pearson's correlations were calculated to examine associations between CAR and age. Analyses were repeated with potential confounders as control factors. Results not only demonstrated increased CARs in female individuals with BPD compared to HC but demonstrated elevated CARs with increasing age in BPD individuals exclusively. Effects remained stable after controlling for potential confounders. Thereby, findings suggest that endocrine alterations in BPD may reinforce with increasing age and BPD chronicity.

Keywords Borderline personality disorder · Aging · Stress · Hypothalamic–pituitary–adrenal axis · Cortisol awakening response

Introduction

Borderline personality disorder (BPD) is a severe and chronic mental disorder, which has been defined by emotion dysregulation, impulsivity, identity disturbance, and

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interpersonal problems (American Psychiatric Association 2013). Several BPD symptoms, such as inappropriate and intense anger, stress-associated dissociation or self-harm, are linked to altered stress vulnerability and can possibly be attributed to changes in hypothalamus–pituitary–adrenal (HPA) axis functioning, which is one of the major endocrine stress systems. A common marker of the HPA axis is the cortisol awakening response (CAR), which usually rises steeply in the morning after awakening and proceeds according to a diurnal rhythm (Edwards et al. 2001; Pruessner et al. 1997). Deviations from the typical CAR pattern due to psychosocial, psychiatric and health-related parameters, such as psychosocial stress, are presumed to mirror maladaptive neuroendocrine processes (Clow et al. 2004; Schmidt-Reinwald et al. 1999).

In general, HPA axis functioning depends on multiple factors and age might be a particularly important one. From a developmental perspective, HPA axis functioning is highly reactive after birth. In childhood, however, the HPA axis can become hyporesponsive to stress (Gunnar and Quevedo 2007). In puberty, HPA axis markers reach levels similar to those in adulthood, though it has been assumed that the HPA axis is 'reprogrammed' based on individual experiences of emotional stress (Quevedo et al. 2012). Besides, existing research suggests that basal cortisol secretion increases with age across the lifespan (Seeman et al. 2001) and that HPA axis dysfunctions may contribute to aging-related diseases such as cognitive deficits in some individuals (Gupta and Morley 2014). Until now, however, little research focused directly on links between age and HPA axis functioning in mental disorders.

Interestingly, existing research further suggests that mental disorders can be characterized by "accelerated aging", which means that certain biological correlates amplify with increasing illness duration. For instance, Wolkowitz et al. (2010) highlighted that in depression, stronger alterations of HPA axis functioning over time are accompanied by increased cell damaging processes, immune dysregulation, and oxidative stress. Similarly, Miller and Sadeh (2014) reviewed existing evidence on the "accelerated aging" hypothesis in post-traumatic stress disorder (PTSD) and reported that chronic and repeated activation of the HPA axis—for example, when re-experiencing traumatic experiences—has deleterious effects on the brain, such as hippocampal atrophy and neuronal cell death. In short, altered HPA axis functioning may be related to chronification of mental disorders and it seems likely that comparable links exist between aging and HPA axis functioning in BPD. Yet, the time course between HPA axis functioning and aging needs to be examined in greater detail, in particular for patients with BPD.

With regard to BPD in particular, research demonstrated increased CARs in adult patients (Lieb et al. 2004; Rausch et al. 2015), which can possibly be attributed to individuals with BPD experiencing more daily hassles and inner tension during the day (Jovev and Jackson 2006). Further, it has been shown that individuals with BPD with histories of childhood abuse are at high risk for revictimization as adults, and this might play an important role in maintenance or chronification of stress vulnerability (Paris and Zweig-Frank 1992). For adolescents, previous research revealed that CARs were higher in individuals with histories of childhood maltreatment and pronounced BPD symptoms than in individuals with childhood maltreatment but without BPD symptoms (Kaess et al. 2017). Compared to healthy controls (HC), CARs were also increased in adolescents engaging in non-suicidal self-injury (NSSI), which is an important precursor of BPD development (Reichl et al. 2016). Taken together, previous findings suggest that BPD pathology is related to HPA axis alterations (i.e., increased CAR), though it has not been investigated whether this association varies for different age groups.

Based on existing research, the present study, therefore, investigated if individuals with BPD display elevated CARs, even when a broader age range is examined than in previous studies. Correspondingly, we hypothesized that individuals with BPD would display an elevated CAR compared to healthy controls. Moreover, associations between age and CAR in individuals with BPD were examined in particular. Owing to the notion that BPD can be seen as a life span disorder and frequently chronifies due to frequent revictimization, daily hassles and other stressful experiences, we hypothesized that individuals with BPD would display an even more increased CAR with older age.

Methods

Participants

Participants were 54 female individuals with a current diagnosis of BPD according to the diagnostic criteria of DSM-IV (BPD; $M_{age} = 23.7$ years, SD = 6.5, range: 15–40 years) and 54 female age-, and intelligence-matched[1] healthy controls (HC; $M_{age} = 23.0$, SD = 7.4, range: 15–48 years), who had never received a psychiatric diagnosis or undergone any psychological or psychiatric treatment (see Table 1 for details on sample characteristics including comorbid disorders). Participants were recruited through the resident's registration office, advertisements and clinical referral from in- and outpatient units. General exclusion criteria comprised current substance abuse (urine screening), substance abuse in

[1] Raven's Progressive Matrices were used an estimate for intelligence (John and Raven 2003).

Table 1 Demographic and clinical data of patients with borderline personality disorder (BPD) and healthy controls (HC)

	BPD patients [$M \pm$ SD; n (%)]	Range	Healthy controls [$M \pm$ SD; n (%)]	Range	t/χ^2	p
Age (years)	23.7 ± 6.5	[15, 40]	23.0 ± 7.4	[15, 48]	0.51	0.611
Body Mass Index (kg/m^2)	23.5 ± 5.3	[18.59, 38.30]	22.9 ± 4.1	[18.34, 37.23]	1.57	0.120
Smokers (n)	20 (37%)		8 (15%)		6.94	0.008
Oral contraceptive use (n)	12 (22%)		27 (50%)		9.03	0.003
Regular medication[a]	4 (7%)		0		4.15	0.042
Time of awakening	0702 h ± 1.5 h		0747 h ± 1.4 h		2.46	0.120
Sleep duration (hours)	7.9 ± 1.3	[4, 10]	8.1 ± 1.1	[5.5, 10.75]	− 0.98	0.332
Childhood traumatization (CTQ Total Score)	56.6 ± 18.1	[25, 116]	31.6 ± 10.8	[25, 81]	8.39	< 0.001
Depressiveness (BDI-II Score)	26.7 ± 11.0	[0, 52]	3.1 ± 3.4	[0, 20]	14.52	< 0.001
Borderline symptom severity (BSL-23 Score)	2.1 ± 0.9	[0, 3.65]	0.1 ± 0.1	[0, 0.65]	16.14	< 0.001
No. of DSM-IV BPD criteria	6.3 ± 1.5	[5, 45]	0	[0, 3]		
Current major depression (n)	14 (26%)		0			
Lifetime major depression (n)	39 (72%)		0			
Current post-traumatic stress disorder (n)	12 (22%)		0			
Lifetime post-traumatic stress disorder (n)	14 (26%)		0			

M mean, *SD* standard deviation, *BSL-23* borderline symptom list, *BDI-II* Beck Depression Inventory-II, *CTQ* Childhood Trauma Questionnaire

[a]One patient was treated with Fluoxetine, one with Fluoxetine and Lorazepam, one with Fluoxetine and Fenofibrate, and one with Agomelatine

the past two months (interview), and severe medical illness. Individuals with BPD were additionally excluded when presenting with a lifetime diagnosis of schizophrenia, schizoaffective or bipolar disorder, or substance dependence in the past year. The study was part of the KFO-256 (Schmahl et al. 2014), a German consortium on mechanisms underlying emotion dysregulation in BPD.[2] Sensitivity analyses indicated that the included sample was large enough to detect small group differences of $d \geq 0.58$ in AUC_G of the CAR as reported in our former study (Rausch et al. 2015) with a power of 1-ß ≥ 0.80. Data partly overlap with data published by Rausch et al. (2015); however, the current research question has not been addressed by a previous publication by the consortium. The Ethics Committee at Heidelberg University approved the study. Participants signed written informed consent and received a financial compensation. Written informed consent was also obtained from all parents or legal guardians if they were minors.

Measures

Axis I disorders were assessed by qualified diagnosticians using the Structured Clinical Interview for DSM-IV (SCID-I; First and Gibbon 2004). BPD, avoidant PD and antisocial PD were examined using the International Personality Disorder Examination (IPDE; Loranger et al. 1994). Interviews were performed by experienced diagnosticians, who had at least a master's degree in psychology or medical doctorate and underwent standardized training resulting in high interrater reliability (ICC ≥ 0.091 for the number of BPD criteria). Additionally, BPD symptom severity was examined using the short version of the Borderline Symptom List (BSL-23; Bohus et al. 2009), depressiveness using the Beck Depression Inventory (BDI-II; Beck and Steer 1984), and history of childhood traumatization using the Childhood Trauma Questionnaire (CTQ; Bernstein et al. 1994). Demographic information was assessed using standardized questionnaires. Height and weight were measured at the day of diagnostic interview.

Cortisol assessment and analysis

Cortisol awakening response

Cortisol awakening response (CAR) was assessed on two consecutive weekdays to get a reliable measure of basal HPA axis activity (Hellhammer et al. 2007). At both days, participants collected saliva samples with salivette devices (Sarstedt, Rommelsdorf, Germany) at home at awakening and 30, 45, and 60 min later by gently chewing on a cotton swab for about 1 min. Saliva sample collection was protocolled and time-locked with electronic monitoring systems [Medication Event Monitoring System (MEMS®)], which are known to enhance compliance of participants

[2] Projects by the KFO include participants recruited by a common recruitment unit with psychometric data of all participants being monitored in a central data bank. Samples across KFO-256 studies may show overlap in participants.

(Kudielka et al. 2012). During sampling periods, participants were instructed to refrain from drinking anything but water, brushing their teeth, eating, and exercising. Samples were stored in refrigerators or freezers until storage in the laboratory and frozen at − 20 °C until biochemical analysis. Cortisol concentration was measured using a commercially available chemiluminescence immunoassay (CLIA) with high sensitivity of 0.16 ng/ml (IBL) and intra- and interassay coefficients of less than 6% and 8%, respectively. Area under the curve with respect to the ground (AUC_G) and mean cortisol increase (MnInc) were computed to estimate trait measures of HPA axis activity.[3] Data were not logarithmized and no participants had to be excluded due to extreme outliers.

Statistical analyses

Statistical analyses were performed with IBM SPSS 22 with α set to 0.05. Table 1 shows demographic and self-report data of BPD individuals and HC based on comparisons using *t*-tests for independent groups and χ^2-tests. Group differences and age effects in cortisol data were examined using a mixed-design analysis of covariance (ANCOVA) with the between-subject factor group (BPD vs. HC), the within-subject factor time after awakening (0, + 30, + 45, + 60 min) and the continuous predictor age. Additional ANCOVAs examining group and age were calculated for AUC_G and MnInc of the CAR. Dunn's multiple comparisons including Bonferroni corrections were used post hoc to examine significant effects of time or group by time; Pearson's correlations were used for analyses examining associations with age. Where appropriate, the Huynh–Feldt procedure was applied to correct for violations of the sphericity assumption. Correlation coefficients were compared using Fisher's *Z*-transformation. ANCOVAs were repeated with potential confounders as control factors [smoking, contraceptive use, medication use, current diagnosis of major depression or PTSD, childhood trauma (CTQ sum scores)]. Effect sizes are reported as proportion of explained variance [partial eta squared (η^2)].

[3] AUC_G, which represents the entire area under the cortisol awakening response with respect to the ground, was calculated according to a formula described by Pruessner et al. (2003). MnInc, which represents cortisol increase after awakening, was calculated with a formula provided by Wust et al (2000). AUC_G and MnInc were calculated for each participant and day and then averaged over 2 days to form reliable indicators of overall cortisol secretory activity and dynamic cortisol responses following awakening.

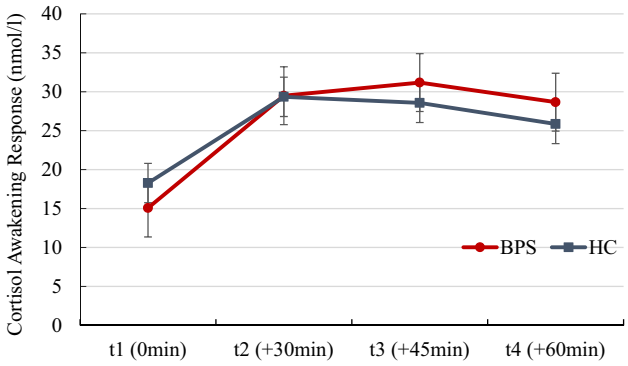

Fig. 1 Cortisol awakening response of patients with borderline personality disorder (BPD) and healthy controls (HC). Standard error is depicted

Results

Descriptively, there was an inverted U-shaped cortisol response after awakening across participants as well as higher cortisol levels in individuals with BPD than in HC across time points (Fig. 1). In line with this, the repeated-measures ANCOVA revealed a significant main effect of time point, [$F(3, 312) = 4.70$, $p = 0.011$, $\eta^2 = 0.04$] with a significant rise from *t*1 (awakening) to *t*2 (+ 30 min, $p < 0.01$), *t*3 (+ 45 min, $p > 0.01$), and *t*4 (+ 60 min, $p < 0.01$) and a significant drop from *t*3 (+ 45 min) to *t*4 (+ 60 min, $p < 0.05$). Furthermore, individuals with BPD tended to show higher cortisol levels than HC in general although this effect was statistically not significant [$F(1,104) = 3.37$, $p = 0.069$, $\eta^2 = 0.03$; Fig. 1].

The group by age interaction [$F(1,104) = 3.91$, $p = 0.051$, $\eta^2 = 0.04$] as well as the group by age by time point interaction [$F(3,312) = 3.65$, $p = 0.029$, $\eta^2 = 0.03$] suggested differential associations between age and cortisol levels in individuals with BPD and HC. In fact, age was positively associated with cortisol levels in individuals with BPD (*t*1: $r = 0.12$, $p = 0.394$, *t*2: $r = 0.30$, $p = 0.030$, *t*3: $r = 0.27$, $p = 0.049$, *t*4: $r = 0.23$, $p = 0.095$), but not in HC (*t*1: $r = 0.06$, $p = 0.682$, *t*2: $r = -0.08$, $p = 0.574$, *t*3: $r = -0.14$, $p = 0.323$, $t4 = r = -0.13$, $p = 0.344$) with significant group differences in correlation coefficients at *t*2 ($z = 1.97$, $p = 0.025$), *t*3 ($z = 2.11$, $p = 0.017$), and *t*4 ($z = 1.84$, $p = 0.033$).

The mean cortisol levels of individuals with BPD and of HC at the different measurement time points after awakening as well as the MnInc of the CAR and the mean AUCG of the CAR of both groups are depicted in Table 2. While analyses failed to reach statistical significance, AUC_G data revealed a similar pattern of results as patients tended to show higher AUC_G [$F(1,104) = 3.51$, $p = 0.064$, $\eta^2 = 0.03$] and a differential association between AUC_G and age than HC [$F(1,104) = 3.88$, $p = 0.051$, $\eta^2 = 0.04$]. AUC_G and age were positively correlated in

Table 2 Mean cortisol levels at awakening (0 min; *t*1) as well as + 30 min (*t*2), + 45 min (*t*3), and + 60 min (*t*4) after awakening (in nmol/l), area under the curve with respect to ground (AUC_G), and mean increase (MnInc) of the Cortisol awakening response of patients with borderline personality disorder (BPD) and healthy controls (HC)

	BPD patients ($M \pm SD$)	Healthy controls ($M \pm SD$)
*t*1 (0 min)	15.1 ± 8.2	18.3 ± 8.2
*t*2 (+ 30 min)	29.5 ± 14.5	29.3 ± 13.6
*t*3 (+ 45 min)	31.2 ± 15.1	28.6 ± 14.6
*t*4 (+ 60 min)	28.7 ± 15.0	25.9 ± 12.4
AUC_G	1572.0 ± 720.8	1556.8 ± 684.8
MnInc	14.7 ± 12.3	9.6 ± 9.9

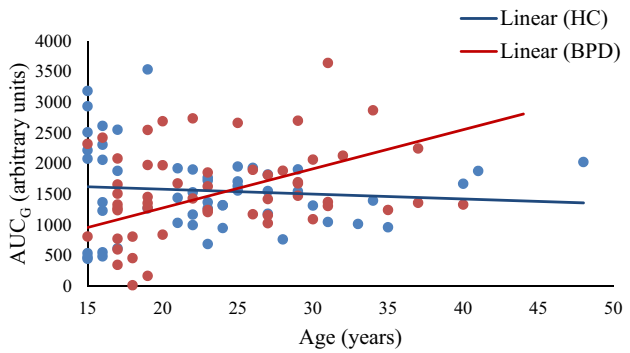

Fig. 2 Association between area under the curve with respect to ground (AUC_G) of the cortisol awakening response and age in patients with borderline personality disorder (BPD) and healthy controls (HC)

individuals with BPD ($r = 0.28$, $p = 0.044$), but not in HC ($r = -0.09$, $p = 0.536$; group comparison: $z = 1.91$, $p = 0.028$; Fig. 2).

For MnInc, the main effect of group was not statistically significant, [$F(1,104) = 2.53$, $p = 0.115$, $\eta^2 = 0.02$]; however, post hoc tests of the group by age interaction [$F(1,104) = 5.54$, $p = 0.020$, $\eta^2 = 0.05$] showed a positive correlation between age and MnInc in individuals with BPD ($r = 0.24$, $p = 0.081$), but not in HC ($r = -0.09$, $p = 0.536$, group comparison: $z = 1.69$, $p = 0.045$).

Taken together, there was a trend for elevated cortisol awakening responses in individuals with BPD compared to HC, but this effect was qualified by age with greater differences between the BPD and HC group with increasing age. Effects remained stable after controlling for potential confounding effects of medication use, contraceptive use, smoking, current diagnosis of major depression and PTSD as well as childhood trauma (CTQ).

Discussion

This is, to our knowledge, the first study focusing on age-specific endocrine alterations in BPD. Our findings indicate that female individuals with BPD of different ages tend to show increased CARs compared to healthy female controls, which coincides with earlier research on increased salivary cortisol responses to awakening (Carvalho Fernando et al. 2012) and elevated salivary cortisol levels over the day (Lieb et al. 2004). Interestingly, our findings further show that endocrine differences between experimental groups increase with age of individuals, independent of potential confounders. Thus, CARs rose with age of individuals in the BPD group, while staying on a constant level in the control group. Since BPD commonly develops during childhood and adolescence, this could indicate that the duration of BPD symptoms is associated with increasing HPA axis dysfunction and related stress vulnerability. Consequently, a larger CAR with increasing age may be seen as a correlate of BPD chronicity, considering that individuals with BPD report more frequent and intense daily hassles (Jovev and Jackson 2006), display elevated levels of stress associated with inner tension (Kuo and Linehan 2009), and are revictimized more frequently (Paris and Zweig-Frank 1992) over the life course. Consequently, less attenuation of the CAR in older individuals with BPD may be viewed as a neuroendocrine correlate of a long stress-related illness.

Patients with BPD reported significantly more childhood trauma than healthy controls, which is consistent with previous reports on adverse childhood experiences in this patient population (e.g. Infurna et al. 2016). Yet, statistical analyses indicated that childhood trauma did not confound the association between experimental group and CAR, which coincides with earlier research showing only weak positive associations between self-reported childhood trauma and basal saliva cortisol levels in BPD (Carvalho Fernando et al. 2012), partially replicating own results (Rausch et al. 2015). The current study also matches with research by Reichl et al. (2016), who demonstrated that childhood adversity differentially affected diurnal slope of the CAR in NSSI patients and healthy controls.

To examine this issue in greater detail, future studies should use longitudinal designs to explicitly investigate associations between age, stress responsivity and altered HPA axis functioning in individuals with BPD over time. A better understanding of age-related diseases seems further crucial as the HPA axis regulates homeostasis, for instance within the cardiovascular, neuroendocrine, metabolic or immune system. Future research may, therefore, investigate whether altered HPA axis functioning in individuals with BPD is related to lower physical health (Powers and Oltmanns 2012), i.e., cognitive deficits (Gupta and Morley

2014), Type II diabetes (Frankenburg and Zanarini 2006) or stroke (Chen et al. 2017). This seems particularly relevant given that individuals tend to be at risk for severe physical illness and subsequent mortality (Fok et al. 2014). Finally, future research may also investigate whether alterations of the CAR can be normalized by early treatment of BPD. By way of example, research may investigate if successful treatment leads to a normalization of the HPA axis and whether such a normalization is associated with improved physical and psychological health in general.

When interpreting the current findings, several limitations and strengths of the current study should be considered. First, the study applied a cross-sectional design, which has limited explanatory power given that long-range hormonal changes were investigated. Subsequently, conclusions on associations between age and endocrine functioning in patients with BPD should be interpreted cautiously and require careful replication using longitudinal research. To explore the development of altered HPA axis functioning due to BPD chronicity, further studies may investigate endocrine alterations in patients with BPD of different ages and including dynamic parameters of HPA axis responsiveness such as psychosocial challenges, such as the Trier Social Stress Test (Kirschbaum et al. 1993), or pharmacological challenges, such as the dexamethasone suppression test, which potentially enables a differentiated profile of HPA axis functioning in individuals with BPD. To date, meta-analytic research indicated that especially psychosocial challenges and continuous cortisol measures—such as the CAR—are altered in individuals with BPD (Drews et al. 2019). Here, cortisol profiles seem to be blunted in response to psychosocial challenges but elevated based on continuous measures when using healthy individuals as comparison. Furthermore, the experimental design rendered inclusion of male individuals with BPD impossible, so that the current findings may not be generalized to male patients with BPD (Seeman et al. 2001). Since only females were included for the current sample, it needs to be mentioned that menstrual cycle has not been assessed systematically. We can, therefore, not exclude the possibility that menstrual cycle influenced associations between CAR and psychopathology. Yet, existing studies indicate that menstrual cycle does not significantly affect such an association (Kirschbaum et al. 1999; Kudielka et al. 2003; Wust et al. 2000). This notion is further supported by a recent meta-analysis on HPA axis functioning in individuals with BPD, which could not find any significant gender differences using meta-regressions (Drews et al. 2019) Nonetheless, future studies may systematically assess and analyze menstrual cycle to examine the influence of this variable more closely. With regard to strengths of the current study, this is one of the few studies covering a wide age range in adults and adolescents with BPD, which allowed for a thorough investigation of associations of age and HPA axis activity. Moreover, the reliable ambulatory assessment enabled precise and comprehensive measurements and analyses were controlled for a broad range of potential confounders.

Taken together, the present study not only suggests differential CAR levels in individuals with BPD and healthy controls but further indicates close links between aging and HPA axis dysfunction in individuals with BPD. Possibly, these alterations are related to enhanced anticipation of upcoming stressors with increasing age, which in turn, indicates an important connection with BPD chronicity. Additionally, altered CAR levels may have far-reaching consequences for several physical health conditions. To further investigate this issue, future studies should not only include larger adolescent samples and apply longitudinal designs but may additionally focus on whether preventive interventions translate into alterations of the neuroendocrine stress response in individuals with BPD.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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Hypothalamic-pituitary-thyroid axis function in female adolescent nonsuicidal self-injury and its association with comorbid borderline personality disorder and depression

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ABSTRACT

Objectives: Behavioral disturbances in adolescence are potentially linked to aberrant functioning of the thyroid gland. Accordingly, alterations of the hypothalamic-pituitary-thyroid (HPT) axis might impact psychopathological development. Yet corresponding research in adolescents with nonsuicidal self-injury (NSSI) and comorbid mental disorders is scarce.

Methods: The present study examined HPT axis functioning in adolescents with NSSI compared to healthy controls (HC) using blood-based assays of thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), and the ratio of these hormones (fT3/fT4 ratio). Cortisol was additionally examined to contrast HPT axis functioning with a well-established biomarker of stress responsivity. Moreover, associations between clinical characteristics, HPT axis and HPA axis functioning were investigated. Female adolescents meeting NSSI criteria according to DSM-5 criteria ($n = 117$) were compared to adolescent HC ($n = 41$). Standardized serum-based endocrinological assays and interview- and questionnaire-based psychiatric assessments were used. Smoking status was included as covariate for all analyses.

Results: NSSI patients displayed altered HPT axis functioning as fT3/fT4 ratio values were blunted in comparison to HC. Negative correlations were further present between fT3, fT3/fT4 ratio and severity of BPD symptoms, depression scores and symptomatic distress. TSH correlated negatively with severity of BPD symptoms and symptomatic distress exclusively. Cortisol values differed neither significantly between experimental groups nor correlated significantly with clinical characteristics.

Conclusions: Longitudinal examinations, assessing links between psychopathology and endocrinological alterations, are warranted to address potential clinical implications of thyroid markers in child and adolescent psychiatry.

1. Introduction

Nonsuicidal self-injury (NSSI) is a serious and common phenomenon in adolescence. Consequently, NSSI has been introduced as a disorder warranting further research in the 5th version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013). Proposed criteria include intentional and self-inflicted damage to the surface of one's body without suicidal intent on five or more days within a year. Epidemiological research estimated that *single events of NSSI* occur in 17% of adolescent nonclinical samples while 5% even meet criteria for *NSSI disorder* (NSSID) (Swannell et al., 2014). NSSI is often accompanied by comorbid disorders such as

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borderline personality disorder (BPD) or major depressive disorder (MDD) (Ghinea et al., 2020). Both disorders emerge commonly during adolescence and include severe emotion dysregulation. Existing evidence suggests that NSSI may serve as a coping strategy to diminish the intensity of negative emotions (Klonsky et al., 2014). Taken together, research shows that NSSI, BPD and depression are common phenomena in adolescence, yet biological markers potentially underlying these psychopathologies have been investigated insufficiently.

To investigate somatic correlates of psychiatric disorders, there has been a growing interest in endocrinological markers, such as hormones of the hypothalamic-pituitary-adrenal (HPA) axis. A closely related axis, the hypothalamic-pituitary-thyroid (HPT) axis, has received far less interest, although it can be assumed that HPT axis functioning influences psychosocial health significantly. Here, thyrotropin-releasing hormone (TRH) stimulates secretion of thyroid-stimulating hormone (TSH) in the anterior pituitary gland, which prompts triiodothyronine (T3) and thyroxine (T4) secretion in the thyroid gland. T3 and T4 are available in free form (fT3; fT4) or attached to proteins. And importantly, thyroid hormones do not only regulate the metabolism, but also impinge upon the cardiovascular system, bone maintenance, pregnancy outcomes, child development, and mental health.

Given the absence of research investigating HPT axis hormones in NSSI, the present study aimed at investigating HPT axis functioning in adolescents engaging in NSSI compared with healthy controls (HC). Based on prior research in BPD and MDD, NSSI patients were expected to show altered HPT axis hormones (i.e. elevated TSH and decreased fT3, fT4, fT3/fT4 ratio). Additionally, cortisol, the primary marker of the HPA axis, was included to reassess links between psychopathology and endocrinological functioning more generally. Lastly, we investigated whether comorbid psychopathological characteristics, i.e. severity of BPD and depression as well as symptomatic distress, would correspond to stronger blunting of HPT axis hormones or cortisol.

2. Methods

2.1. General procedures and participants

Data for the present analyses were collected drawing on a consecutive help-seeking cohort of adolescents (12–17 years) presenting at the outpatient clinic for adolescent risk-taking and self-harm behavior (*AtR!Sk*; Ambulanz für Risikoverhalten und Selbstschädigung) at the Clinic for Child and Adolescent Psychiatry, University Hospital Heidelberg. Patients underwent a first-stage, structured psychiatric diagnostic assessment (ethical approval: ID S-449/2013) followed by the invitation to participate in a second appointment involving various neurobiological assessments (*AtR!Sk-Bio*; ethical approval: ID S-514/2015). NSSI patients were included when reporting acts of nonsuicidal self-injury on at least five days in the past 12 months, as defined by the DSM-5 criterion A (American Psychiatric Association, 2013). Intention of self-injury as "nonsuicidal" was explicitly required to avoid conceptual overlap between NSSI and suicide attempts. Patients showing acute psychotic symptoms or insufficient speech comprehension were excluded. HC were only included when history of NSSI, endorsement of psychiatric disorder and corresponding treatments could be excluded prior to participation in the study. Patients and their legal guardians signed written informed consent to participate in both assessments. Both studies were carried out in accordance with the declaration of Helsinki.

The manuscript reports on cross-sectional data from *AtR!Sk-Bio*, which was implemented in 2016, in combination with *AtR!Sk* clinical data. Recruitment for *AtR!Sk-Bio* took place within 6 weeks after the diagnostic assessment in *AtR!Sk*. HC were recruited via public advertisement and underwent an adapted form of the diagnostic assessment prior to being invited to *AtR!Sk-Bio*. For *AtR!Sk-Bio*, height (cm) and weight (kg) were measured after a structured assessment on fasting status, handedness, smoking status, present-day coffee consumption, menstrual status, contraception use, physical illnesses, and medication use. Subsequently, fasting blood samples were taken by qualified medical staff. HPT axis hormones and cortisol were examined using standardized serum-based blood draws. Preanalytical variation was minimized by performing venipuncture in a standardized manner around 0900 h. After blood collection, samples were immediately frozen in aliquots at −80 °C until analyzed. Participants received an allowance of 40€ for participation.

2.2. Measures

2.2.1. Psychological instruments

The diagnostic procedures have been described in detail by Kaess and colleagues (Kaess et al., 2017). Frequency and severity of NSSI and suicidality were examined separately using the *Self-Injurious Thoughts and Behaviours Interview* (SITBI-G) (Fischer et al., 2014). BPD diagnoses were based on the *Structured Clinical Interview for DSM-IV Personality Disorders* (SKID-II) (First et al., 1997). Current and lifetime Axis I disorders were assessed with the Mini *International Neuropsychiatric Interview for Children and Adolescents* (MINI-KID) (Sheehan et al., 2010). Depressive symptoms were assessed based on self-reports using the *Depression Inventory for Children and Adolescents* (DIKJ) (Stiensmeier-Pelster et al., 2000). Symptomatic distress was examined based on the *Global Severity Index (GSI)* of the *Symptom-Checklist-90-Revised* (SCL-90-R) (Derogatis and Savitz, 1999). Adverse childhood experiences (ACEs) were examined using the *Childhood Experience of Care and Abuse Questionnaire* (CECA.Q) (Smith et al., 2002). The self-report questionnaire was used to examine lack of parental care (i.e. neglect and antipathy), parental physical abuse, and sexual abuse from any adult before age 17. German versions were used for all questionnaires and interviews.

2.2.2. Endocrinological assays

Baseline thyroid function was evaluated based on TSH, fT3, fT4 and fT3/fT4 ratio. The reference range was 0.4–4.0 mU/l for TSH, 2.0–4.2 ng/l for fT3, and 8–18 ng/l for fT4. The intra-assay coefficient of variation (c.v.) was 2.41–2.48% for TSH, 2.35–3.08% for fT3, and 2.23–3.33% for fT4. The inter-assay c.v. was 2.05–5.31% for TSH and 2.33–4.00% for fT4. Baseline HPA axis functioning was examined using cortisol. The reference range was 56–200 ng/ml. The intra-assay c.v. was 2.9–4.2%. The inter-assay c.v. was 4.4–6.0%. Fasting blood samples were thawed and analyzed by immunoassays (ADVIA Centaur® Assay). No prior thawing of the frozen plasma samples was performed. Blood analyses were conducted according to accredited routines at the central laboratory of the University Hospital Heidelberg.

2.3. Statistical analyses

Adolescents reporting ≥5 acts of NSSI within the past year were included for the NSSI group, adolescents without history of NSSI were included for the HC group. Sociodemographic and clinical differences between groups were compared using *t*-tests for dimensional variables and χ^2-tests for categorical variables. Groups differed significantly with regard to smoking status ($p = .005$), which was therefore included as covariate to all subsequent analyses. Groups differed also with regard to school type ($p = .027$), however, there were no significant relationships with endocrinological parameters. As all variables other than smoking neither correlated with experimental groups nor biological markers, they were not included as covariates in the statistical analyses. Group differences on endocrinological parameters were analyzed using regression analyses. Associations between hormonal and clinical characteristics were analyzed using Pearson's correlations. Subsequently, semipartial correlations were run to determine the relationship between endocrinological markers and psychopathology whilst controlling for smoking status. Statistical analyses were performed using STATA (*Stata Statistical Software: Release 15*, 2017, StataCorp LP, College Station, TX, USA) with α set to 0.05.

3. Results

3.1. Sociodemographic and clinical characteristics

The study sample comprised $n = 117$ NSSI patients and $n = 41$ HC (see Supplement 1 for in- and exclusion criteria and sociodemographic characteristics). NSSI patients smoked more frequently in the past month ($p = .005$) and attended lower school types than HC ($p = .027$). Groups did not differ on age, body weight, body height, body mass index (BMI), average physical activity per week, estradiol levels, menstrual status, hormonal contraceptive use, medical condition within the past 3 months, alcohol consumption, or illicit drug use (all $p \geq .117$). Comorbid diagnoses, clinical characteristics, as well as frequency of ACEs are shown in Supplement 2. Approximately one third of the NSSI group ($n = 34$; 29%) met at least five BPD criteria in the clinical interview; diagnostic criteria for depression were met by $n = 72$ (62%). Besides, NSSI patients reported a significant higher frequency of ACEs in general ($p < .001$) and also scored higher on several subscales of the CECA.Q, i.e. parental antipathy ($p < .001$), parental neglect ($p < .001$), and sexual abuse from any adult before age 17 ($p < .001$). Traumascores, which were calculated based on frequency and severity of ACEs, were positively correlated with number of BPD criteria ($p = .013$), depression scores ($p = .024$) and suicide attempts in the past 12 months ($p = .017$). Traumascores were neither correlated with GSIs ($p = .081$) nor with frequency of nonsuicidal self-injury in the past 12 months ($p = .382$).

3.2. Hormonal levels

As shown in Table 1, groups differed significantly with regard to fT3/fT4 ratio. Ratio values were lower in NSSI patients ($M = 0.30$, $SD = 0.05$) than in HC ($M = 0.32$, $SD = 0.05$). For fT3, the regression model was significant ($p = .004$), yet groups did not differ significantly ($t_{(156)} = -1.78$, $p = .77$).

3.3. Associations between clinical characteristics and hormone levels

As shown in Table 2, BPD severity correlated negatively with TSH ($p = .027$), fT3 ($p = .009$), fT3/fT4 ratio ($p = .009$), and smoking status ($p < .001$). As shown in Table 3, semipartial correlations for BPD severity were significant for TSH ($p = .013$) and fT3/fT4 ratio ($p = .009$). Depression severity correlated negatively with fT3 ($p = .008$), fT3/fT4 ratio ($p = .003$), and smoking status ($p = .034$). Semipartial correlations for depression severity were significant for fT3 ($p = .019$) and smoking status ($p = .020$), as well as fT3/fT4 ratio ($p = .003$). Symptomatic distress correlated negatively with TSH ($p = .014$), fT3 ($p = .017$) and fT3/fT4 ratio ($p = .003$). Semipartial correlations for symptom distress were significant for TSH ($p = .022$), fT3 ($p = .026$) and smoking status ($p = .010$), as well as fT3/fT4 ratio ($p = .002$).

Table 1
Group differences on thyroid markers and cortisol.

Biomarker	NSSI	HC	Comparison			
	Mean ± SD	Mean ± SD	*F*	*p*	Adj. R^2	*ES*
TSH (mU/l)	2.16 ± 1.05	2.31 ± 1.18	0.59	0.557	< −0.01	0.06
fT3 (ng/l)	3.38 ± 0.35	3.53 ± 0.42	5.81	0.004	0.06	0.57
fT4 (ng/l)	11.52 ± 1.50	11.07 ± 1.21	2.69	0.071	0.02	0.39
fT3/fT4 ratio	0.30 ± 0.05	0.32 ± 0.05	5.46	0.005	0.06	0.56
Cortisol (ng/ml)	161.55 ± 66.22	175.73 ± 71.45	2.19	0.116	0.02	0.01

Note. Sample sizes for all TSH, fT3, fT4, and fT3/fT4 ratio were $n = 117$ for NSSI patients and $n = 41$ for HC. Degrees of freedom (*df*) were (2, 141) for these endocrinological markers. Sample sizes for cortisol were $n = 110$ for NSSI patients and $n = 39$ for HC. Degrees of freedom (*df*) were (2,132) for cortisol. Nicotine use in the past month (yes/no) was included as covariate. Due to reasons of space, statistics for these covariates are not shown but available on request. TSH = thyroid-stimulating hormone; fT3 = free triiodothyronine; fT4 = free thyroxine; fT3/fT4 ratio = ratio between free triiodothyronine and free thyroxine.

Table 2
Partial correlations between endocrinological markers and clinical characteristics for the full study sample.

Biomarker	No. BPD criteria (SCID-II)		Depression score (DIKJ)		Global Severity Index (SCL-90-R)	
	$n = 158$		$n = 144$		$n = 145$	
	r	*p*	*r*	*p*	*r*	*p*
TSH (mU/l)	−0.176	0.027*	−0.097	0.250	−0.203	0.014*
fT3 (ng/l)	−0.206	0.009**	−0.221	0.008**	−0.198	0.017*
fT4 (ng/l)	0.072	0.367	0.123	0.143	0.139	0.096
fT3/fT4 ratio	−0.206	0.009**	−0.249	0.003**	−0.246	0.003**
Cortisol (ng/ml)	−0.020	0.809	−0.115	0.183	−0.087	0.313
Smoking (yes/no)	0.401	< 0.001***	0.186	0.034*	0.114	0.192

Note. SCID-II = Structured Clinical Interview for DSM-IV Personality Disorders; DIKJ = Depression Inventory for Children and Adolescents. SCL-90-R = Symptom-Checklist-90-Revised. Cortisol samples were available for $n = 149$ participants for correlation analyses with BPD criteria, for $n = 135$ participants for correlation analyses with depression scores, and for $n = 136$ participants for correlation analyses with global severity indices. Details related to smoking status were available for $n = 144$ participants for correlation analyses with BPD criteria, for $n = 131$ participants for correlation analyses with depression scores, and for $n = 132$ participants for correlation analyses with global severity indices. *$p < .05$, **$p < .01$, ***$p < .001$.

4. Discussion

The current study examined HPT axis hormones in adolescents with NSSI compared to healthy controls. Above all, findings suggest that altered fT3/fT4 might be a biological correlate of NSSI in adolescence, which in turn might indicate disrupted conversion from T4 to T3 in NSSI patients. Abnormal conversion from T4 to T3 may lead to fatigue, depression, and difficulty concentrating, which suggests that these symptoms should be taken seriously during physical examinations of NSSI patients. In this context, one may further question whether a higher frequency of NSSI coincides with stronger endocrinological alterations. Yet, our results suggest no such association and exploratory analyses assessing links between frequency of NSSI and thyroid markers failed to reach statistical significance. However, as we investigated a clinical help-seeking sample presenting with severe and repetitive NSSI, findings might not generalize to population- or college-based samples frequently studied in the field. Put differently, as a higher frequency of NSSI is associated with greater psychopathological distress, our findings might not generalize to occasional NSSI, which has not readily been captured in the present sample. However, and given the heterogeneity of NSSI frequency in the present sample, it seems rather unlikely that the inclusion of patients with low to mild NSSI frequency would have challenged these findings. Additionally, most endocrine markers were in the normal physiological range in the current study. Yet, HPT axis markers have relatively fixed *individual* setpoints, which tend to be stable over lifetime (Medici et al., 2015). As our analyses showed that NSSI patients reported more frequent and severe adverse childhood experiences and as these were further associated with BPD severity and suicide attempts in the past year, it might be particularly important to examine long-term relationships between psychopathology and HPT axis alterations to investigate whether such early experiences lead to changes in individual HPT axis setpoints. And, as setpoints can be affected by factors such as inflammation and lack of sleep, a normalization of HPT axis functioning resulting from psychosocial stabilization, for instance due to psychotherapy, needs to be investigated in future studies. Taken together, the

Table 3
Semipartial correlations between endocrinological markers and clinical characteristics for the full study sample.

Biomarker	No. BPD criteria (SCID-II)				Depression score (DIKJ)				Global Severity Index (SCL-90-R)			
	$n = 158$				$n = 144$				$n = 145$			
	Clinical		Smoking		Clinical		Smoking		Clinical		Smoking	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
TSH (mU/l)	−0.208	0.013*	0.134	0.105	−0.095	0.285	0.030	0.735	−0.200	0.022*	0.040	0.645
fT3 (ng/l)	−0.153	0.061	−0.154	0.059	−0.200	0.019*	−0.199	0.020*	−0.188	0.026*	−0.218	0.010*
fT4 (ng/l)	0.119	0.158	−0.084	0.317	0.149	0.090	−0.060	0.496	0.165	0.060	−0.054	0.534
fT3/fT4 ratio	−0.215	0.009**	−0.032	0.692	−0.261	0.003**	−0.085	0.314	−0.265	0.002**	−0.103	0.222
Cortisol (ng/ml)	−0.091	0.290	0.172	0.046*	−0.125	0.167	0.148	0.105	−0.080	0.378	0.134	0.140

Note. SCID-II = Structured Clinical Interview for DSM-IV Personality Disorders; DIKJ = Depression Inventory for Children and Adolescents. SCL-90-R = Symptom-Checklist-90-Revised. Details related to smoking status were available for $n = 144$ participants for correlation analyses with BPD criteria, for $n = 131$ participants for correlation analyses with depression scores, and for $n = 132$ participants for correlation analyses with global severity indices. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$.

current findings are in line with empirical evidence, however, antecedents leading to altered HPT functioning in adolescent NSSI patients need to be examined in greater detail.

Second, negative associations could be demonstrated for focal clinical characteristics and HPT markers. Here, BPD severity predicted blunting of TSH, fT3 and fT3/fT4 ratio, while depression severity predicted blunting of TSH and fT3/fT4 ratio. Symptomatic distress predicted blunting of TSH, fT3 and fT3/fT4 ratio. As suggested by Duval and colleagues (Duval et al., 2010), blunted thyroid levels may either originate from a downregulation of TRH receptors of the pituitary thyrotrophs secondary to a prolonged increase in hypothalamic TRH stimulation or from previously increased thyroid hormone levels and subsequent negative feedback of the HPT axis, which in turn could be associated with more pronounced psychopathology. Since we rely on single assessments, we can only speculate on the underlying cause. In any case, the associations signified in the current study may be linked with emotion dysregulation – commonly underlying NSSI – as thyroid receptors are localized on limbic structures acting on mood regulation (Bauer and Whybrow, 2001). Besides, it has previously been speculated that serotonin (5-hydroxytryptamine; 5-HT) – which likely plays a crucial role with regard to depressive symptoms and BPD (Maurex et al., 2010) – may act peripherally on the thyroid gland and could thereby decrease 5′-deiodinase activity (Sullo et al., 2011). In this context, it has been hypothesized that patients with mood disorders are particularly sensitive to changes in thyroid status, even when peripheral thyroid hormone assays in the normal range (Marangell and Callahan, 1998). This could suggest that even minor deviations of thyroid hormones may parallel markers for psychopathology. To further investigate this hypothesis, it may be worthwhile to investigate if pharmalogical treatment of 5-HT receptors comes along with an increase of thyroid hormones and clinical characteristics.

The finding that most endocrinological markers were not directly associated with NSSI behavior but rather with general psychopathology (such as symptomatic distress) further suggests that HPT axis dysfunction may present a non-specific mechanism promoting the development and maintenance of NSSI via general psychopathological distress. Recently, we proposed a temporal framework (Kaess et al., 2021), within which neurobiological factors associated with NSSI should be distinguished as (1) *distal biological traits* (e.g. biological predisposition or vulnerability for NSSI), (2) *proximal biological traits* (e.g. biological processes underlying NSSI that are of moderate stability) and (3) *biological states* directly preceding or following NSSI. As such, and based on the present findings, HPT axis dysfunction can be considered a distal biological trait, which is not necessarily linked to NSSI but to functional abnormalities related to the predisposition of the behavior. This hypothesis is further supported by the fact that HPT levels may not change in the short term or transient depending on the current frequency of NSSI. Further longitudinal research is needed, addressing the longitudinal course of HPT axis function in association with psychopathology in those developing or terminating the behavior. And, while findings were consistent with earlier research (Kirkegaard and Faber, 1998; Sinai et al., 2015), we were the first to show that such associations are present at an early developmental stage. However, future studies should examine separate clinical groups to examine the specificity of thyroid hormones, psychopathology, and emotion dysregulation. Here, future studies may also investigate if a higher frequency of NSSI coincides with more pronounced psychopathology to eventually investigate core mechanisms related to altered HPT axis functioning.

Besides, several limitations of the current study need to be acknowledged. First, generalizability with regard to male participants is limited. However, females develop thyroid diseases more frequently (Bauer et al., 2014) and receive NSSI and BPD diagnoses more often (Widiger and Weissman, 1991), which may point to a high ecological validity of our sample. Second, analyses were based on singular endocrinological assessments using blood draws, which necessitates repeated assessments in future studies to confirm the current findings. This seems especially important with regard to cortisol assessments, as prior research has shown that cortisol changes dynamically depending on current stress responsivity, which is why repeated and dynamic measurements may reflect subjective stress levels more adequately (Drews et al., 2019). Third, and notwithstanding that NSSID has been added to the DSM-5 as an independent disorder requiring further research (American Psychiatric Association, 2013), the validity of the diagnosis has only been examined empirically as of recently (Zetterqvist, 2015) and a recent study by our group indicated that NSSID as a stand-alone diagnosis is rare in help-seeking adolescents (Ghinea et al., 2020). As a matter of fact, NSSID is frequently accompanied by several comorbid disorders and marked functional impairments. In order to investigate the validity of NSSI as a stand-alone diagnostic entity, biological studies have the potential to enrich clinical descriptions and can make an important additive contribution to existing studies on the nosology of NSSI as an independent disorder. Our results seem in line with an increasing body of evidence showing that NSSI may rather serve as a transdiagnostic symptom than a distinct disorder given that many of its biological correlates may be driven by underlying psychopathology. Replication studies using thyroid markers as well as related endocrinological markers in larger samples may have sufficient power to facilitate both classification and differentiation of this clinical picture. A strength of the current study lies in its comprehensive link between biological and psychiatric data within a unique patient population. Moreover, the young age of the sample corresponds with little chronification and marginal interference of psychotropic drugs, which complements research on adult patient groups.

In summary, this study highlights potentially altered thyroid functioning in female adolescents with NSSI as well as associations between thyroid functioning and specific clinical characteristics in NSSI. Nonetheless, research based on long-term and dynamic endocrinological assessments is needed to confirm its etiological and diagnostic value. Once the clinical utility of thyroid markers can be demonstrated, parallel effects of altered hormones and psychiatric symptoms present a promising

avenue for further research. Eventually, such research may facilitate efficient treatment options for adolescents engaging in NSSI.

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Ethical statement

The work described has been carried out in accordance with 'The Code of Ethics of the World Medical Association' (Declaration of Helsinki). The manuscript has been written in line with the 'Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals' and authors aimed for the inclusion of representative human populations (sex, age and ethnicity) as per those recommendations. Informed consent was obtained for experimentation with human subjects. Privacy rights of human subjects were observed at all times.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2021.110345.

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Third Manuscript: Supplement 1

Between August 2016 and March 2020, *n*=357 participants could be included for *AtR!Sk*, as patients and their legal guardians signed written informed consent to be included in the scientific evaluation of *AtR!Sk*. Of these, *n*=257 (72%) patients and their legal guardians signed written informed consent to participate in *AtR!Sk-Bio*. 242 patients (94%) were included for the baseline assessment; 15 patients (6%) dropped out prior to the neurobiological assessment. Healthy female adolescents (HC; *n*=104) were recruited via public advertisement and screened from August 2016 to March 2020. HC were excluded when any lifetime psychiatric disorders were diagnosed prior to the neurobiological assessment or when they decided against participation in *AtR!Sk-Bio* (*n*=51; 49%). Four participants (4%) did not provide informed consent for participation in *AtR!Sk-Bio* at the time of data analysis. Additionally, the following participants were excluded prior to carrying out the statistical analyses: participants being older than 17 years (*n*=7), male participants (*n*=44), NSSI patients reporting five or less acts of self-injury within the past year (*n*=32)[9], participants with incomplete endocrinological datasets (*n*=12), participants taking medication affecting HPT axis functioning (*n*=10), participants with non-fasting status (*n*=11), and participants, who smoked prior to the endocrinological assessment (*n*=17). None of the remaining participants was pregnant during the time of the assessment.

[9] defined in accordance with the DSM-5, i.e. endorsement of at least five acts of self-injurious behavior within the past 12 months.

Table 1

Sociodemographic Characteristics of the Study Sample

Measure	NSSI Patients		Healthy Controls		Comparison		
	n	Mean ± SD	*n*	Mean ± SD	*t* / $\chi 2$	*df*	*p*
Age, years	117	14.77 ± 1.47	41	14.78 ± 1.19	0.04	156	.965
Weight, kg	116	61.38 ± 14.71	41	57.53 ± 8.88	-1.58	155	.117
Height, cm	117	165.16 ± 6.61	41	164.20 ± 5.77	-0.83	156	.407
BMI, kg/m^2	116	22.44 ± 4.84	41	21.35 ± 3.18	-1.34	155	.183
Estradiol level	117	86.06 ± 79.74	41	77.29 ± 57.93	-0.65	156	.519
Menstrual status	117	114 (97.44%)	41	41 (100%)	1.07	1	.301
Contraceptives	117	24 (20.51%)	41	6 (14.63%)	0.68	1	.409
School, *n* (%)	117		41		9.16	3	.027
Hauptschule		14 (11.97%)		2 (4.88%)			
Realschule		14 (34.15%)		42 (35.90%)			
Gymnasium		43 (36.75%)		24 (58.54%)			
Other		18 (15.38%)		1 (2.44%)			
Health status	117	19 (16.24%)	41	4 (9.76%)	1.03	1	.311
Drug use, *n* (%)	116		41		2.46	2	.292
Never		85 (73.28%)		34 (82.93%)			
Sometimes		20 (17.24%)		6 (14.63%)			
Min. 1x/month		11 (9.48%)		1 (2.44%)			
Alcohol, *n* (%)	117		41		0.14	2	.932
Never		38 (32.48%)		13 (31.71%)			
Sometimes		42 (35.90%)		16 (39.02%)			
Min. 1x/month		37 (31.62%)		12 (29.27%)			
Smoker, *n* (%)	107	45 (42.06%)	37	6 (16.22)	8.03	1	.005

Note. Values represent means and standard deviations (SD), unless otherwise indicated. *P*-values refer to pairwise comparisons for continuous data or Chi-Square tests for categorical/dichotomous data. BMI = body mass index. Estradiol levels are reported as pg/ml. For menstrual status, the percentage of participants having their menses was indicated. For hormonal contraceptive use, the percentage of participants taking contraceptives was indicated. For school type, the following categories distinguishing secondary schools after four years of elementary school were used: Gymnasium (8 years; provides general university

entrance qualification); Realschule (6 years; intermediate secondary school); Hauptschule (5 years; secondary general school, prepares for vocational training); Other. Health status was coded as having a physical illness for at least one week within the past three months. Illicit drug use was reported for days spent with drug consumption in the past year. Alcohol consumption was reported for days spent with alcohol consumption in the past year. Nicotine use was reported for participants who smoked in the past month.

Third Manuscript: Supplement 2

Table 2A

Comorbid Diagnoses According to the International Classification of Mental and Behavioral Disorders (ICD-10)

ICD-10 code	Comorbid mental and behavioral disorders	*n*	%
F10-F19	Mental and behavioral disorders due to psychoactive substance use	19	16
F30-F39	Mood disorders	72	62
F40-F48	Neurotic, stress-related and somatoform disorders	50	43
F50-F59	Behavioral syndromes associated with physiological disturbances and physical factors	13	11
F60-69	Disorders of adult personality and behavior	45	38
F90-F98	Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	26	22

Note. With regard to clinical characteristics, comorbid diagnoses according to ICD-10 (excluding F00-F09) were common in NSSI patients. None of the NSSI patients received a diagnosis belonging to the following categories: F20-F29, F70-F79, or F80-F89.

Table 2B

Clinical Characteristics of the Study Sample for NSSI Patients and Healthy Controls Separately

Psychopathology	NSSI Patients		Healthy Controls		Comparison			
	n	Mean±SD	*n*	Mean±SD	*t* or χ^2	*p*	*ES*	*95% CI*
BPD criteria (SCID-II)	117	3.35 ± 2.03	41	0.07 ± 0.34	-10.26	< .001	-1.86	[-3.91; -2.65]
Depression severity (DIKJ)	104	30.01 ± 9.12	40	6.5 ± 5.36	-15.30	< .001	-2.85	[-26.54; -20.47]
Global Severity Index (SCL-90-R)	105	1.65 ± 0.70	40	0.22 ± 0.19	-12.71	< .001	-2.36	[-1.65; -1.20]

Note. SCID-II = Structured Clinical Interview for DSM-IV Personality Disorders. DIKJ = Depression Inventory for Children and Adolescents. SCL-90-R = Symptom-Checklist-90-Revised. Effect sizes (ES) are reported using *Cohen's d*. 95% Confidence Intervals (CI) refer to the respective ES. NSSI patients (*n* = 117) reported an average of 67 NSSI-related acts within the past year (*SD* = 74.07), 0.82 suicide attempts within the past year (*SD* = 2.63, *n* = 116), and 1.40 lifetime suicide attempts (*SD* = 5.11; *n* = 116).

Table 2C

Adverse Childhood Experiences for NSSI Patients and Healthy Controls Separately

Score	NSSI Patients		Healthy Controls		Comparison	
	n	Present (%)	*n*	Present (%)	χ^2	*p*
Adverse childhood experiences	105	69 (65.71)	41	4 (9.76)	36.93	< .001
Antipathy	105	55 (52.38)	40	0 (0)	33.76	< .001
Neglect	105	36 (34.29)	40	1 (2.50)	15.40	< .001
Physical abuse	105	19 (18.10)	41	3 (7.32)	2.68	.102
Sexual abuse	104	27 (25.96)	41	0 (0)	13.08	< .001

Note. Adverse childhood experiences were examined using the Childhood Experience of Care and Abuse Questionnaire (CECA.Q). In NSSI patients, severity of adverse childhood experiences (traumascores) correlated with number of BPD criteria measured with the SCID-II (p = .013), DIKJ depressions scores (p = .024), and suicide attempts in the past 12 months (p = .017). Correlations with SCL-90-R Global Severity Index scores (p = .081) and frequency of nonsuicidal self-injury in the past 12 months (p = .382) failed to reach statistical significance. Data are available on request.