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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.

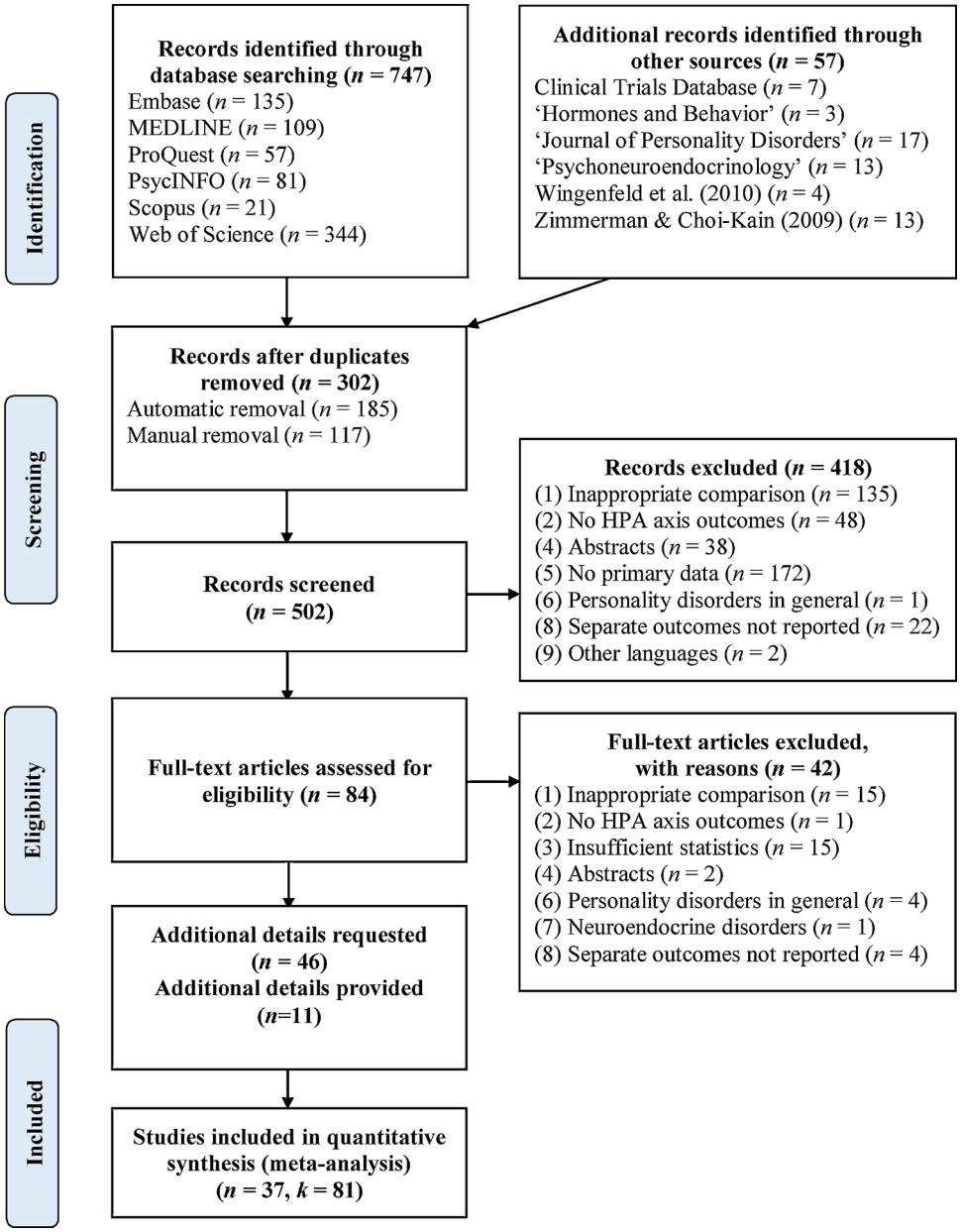

Fig. 1. PRISMA flow diagram illustrating the number of publications identified and the number of publications that were in- and excluded during different stages of the review process.

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

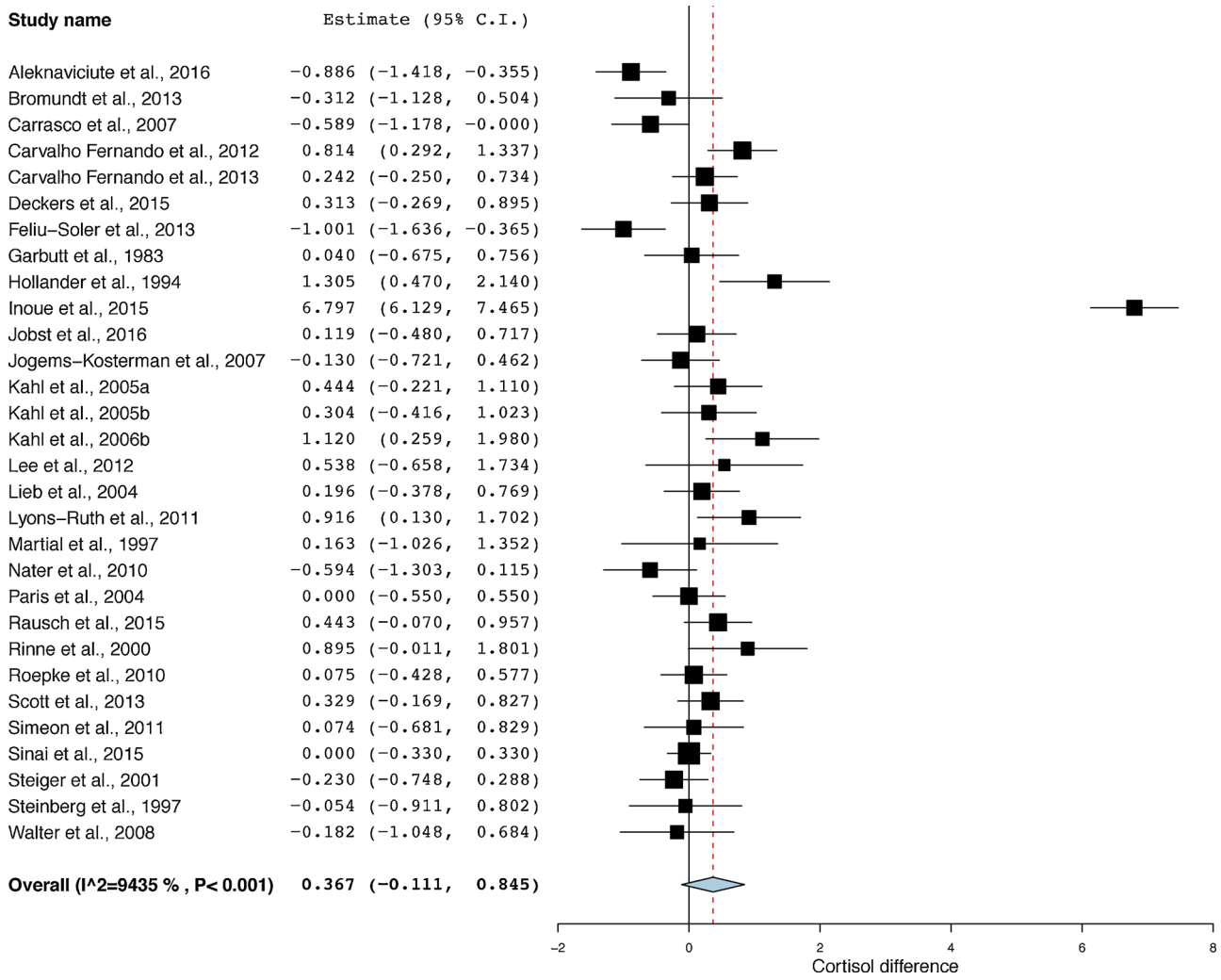

Fig. 2. Forest plot comparing singular cortisol assessments in BPD patients and HC using all available studies.

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.

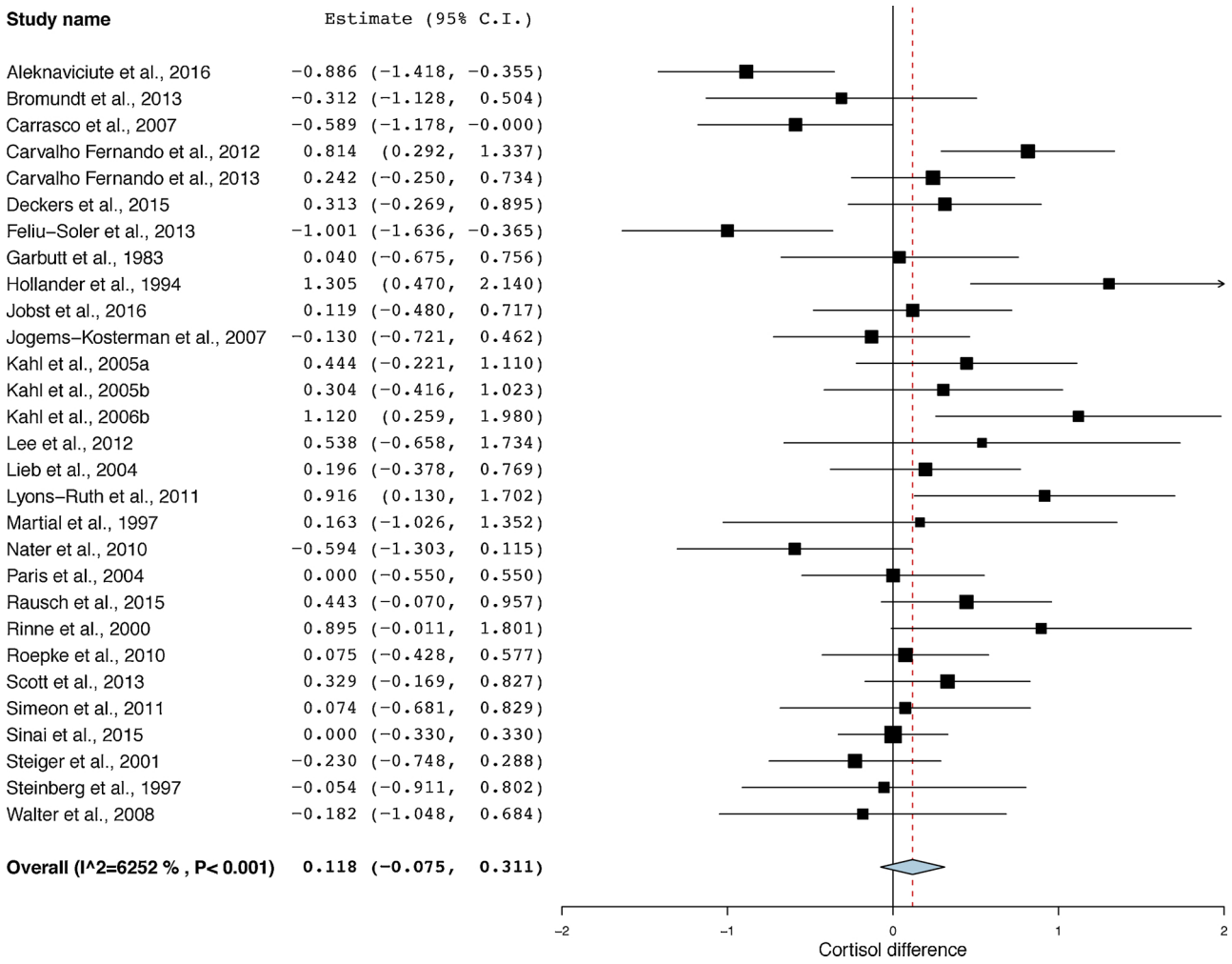

Fig. 3. Forest plot comparing singular cortisol assessments in BPD patients and HC excluding one study (Inoue et al., 2015).

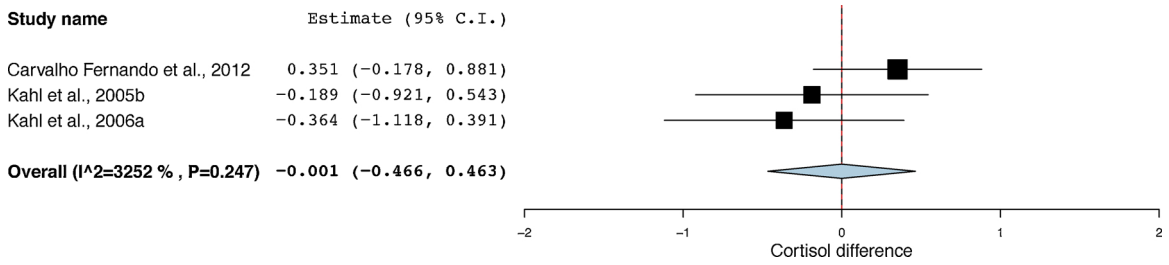

Fig. 4. Forest plot comparing singular cortisol assessments in BPD and MDD patients.

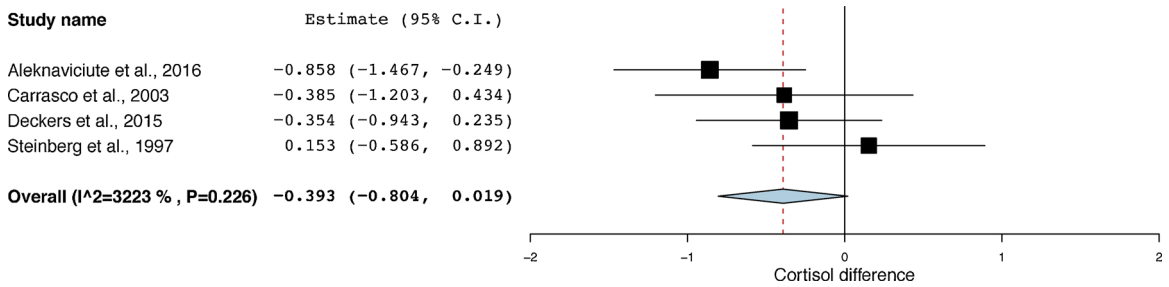

Fig. 5. Forest plot comparing singular cortisol assessments in BPD and patients with other PDs.

(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

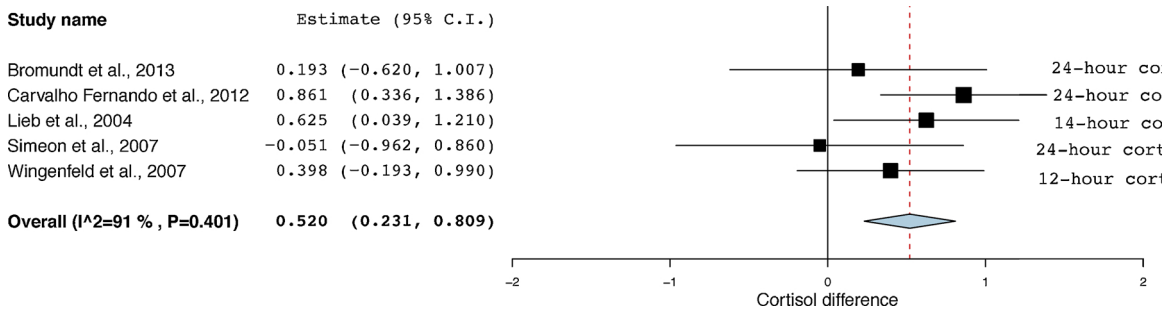

Fig. 6. Forest plot comparing continuous cortisol output in BPD patients and HC. For the studies by Bromundt et al. (2013); Carvalho Fernando et al. (2012) and Lieb et al. (2004), areas under the curve were calculated based on repeated salivary cortisol measures within 14–24 h. Numbers in brackets indicate 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.

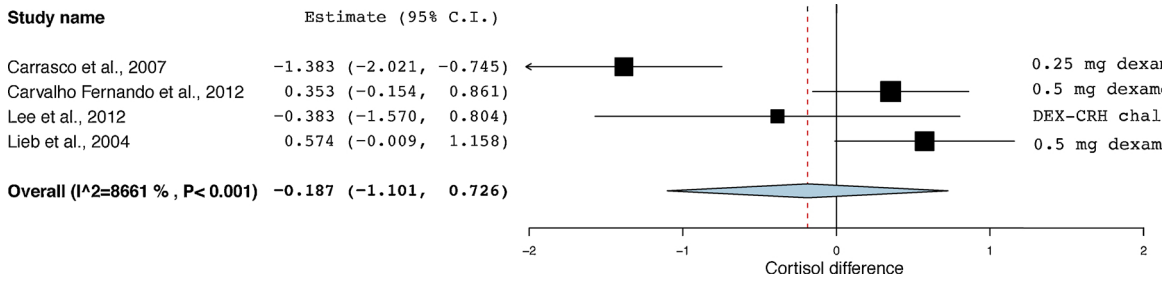

Fig. 7. Forest plot comparing cortisol values after pharmacological challenges in BPD patients and HC. Details on the respective pharmacological challenge are noted on the right side of the figure.

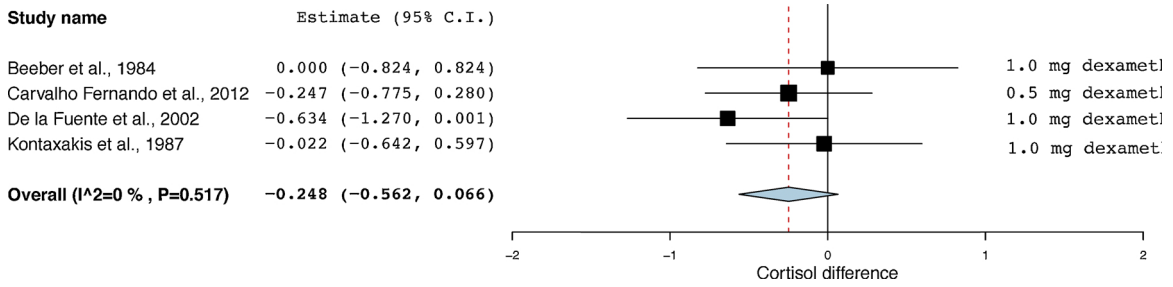

Fig. 8. Forest plot comparing cortisol values after pharmacological challenges in BPD patients and MDD patients. Details on the respective pharmacological challenge are noted on the right side of the figure.

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,

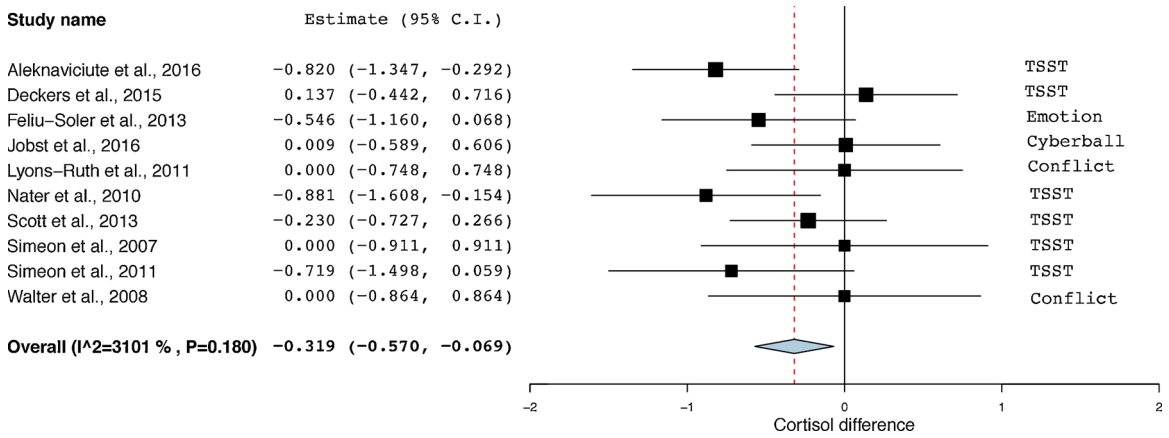

Fig. 9. Forest plot comparing cortisol values during psychosocial stress in BPD patients and HC. Details on the respective psychosocial challenge are noted on the right side of the figure. TSST = Trier Social Stress Test; Emotion = Emotion Induction procedure; Conflict = Conflict Discussion; Cyberball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

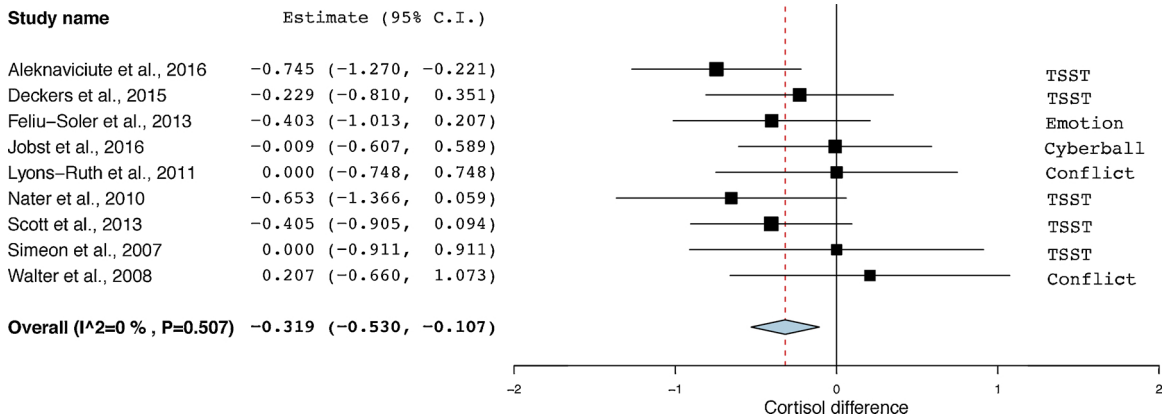

Fig. 10. Forest plot comparing cortisol values after psychosocial stress in BPD patients and HC. Details on the respective psychosocial challenge are noted on the right side of the figure. TSST = Trier Social Stress Test; Emotion = Emotion Induction procedure; Conflict = Conflict Discussion; Cyberball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

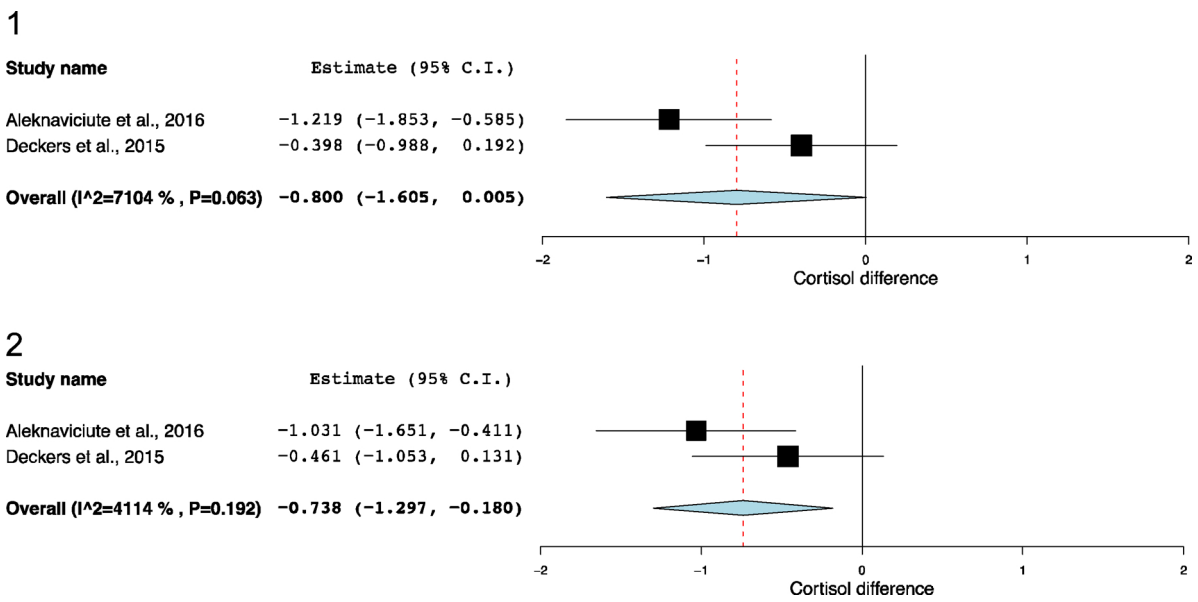

Fig. 11. Forest plots comparing cortisol values during psychosocial stress (11.1) and after psychosocial stress (11.2) in BPD patients and patients with other patients with other Personality Disorders. Both studies applied the TSST.

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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