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Resting State Vagal Tone in Borderline Personality Disorder: *A Meta-Analysis*

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Abstract

Borderline Personality Disorder (BPD) is the most common personality disorder in clinical settings. It is characterized by negative affectivity, emotional liability, anxiety, depression, as well as disinhibition (i.e., impulsivity and risk taking), all of which have been linked to lower resting state vagal tone, which may be indexed by vagally-mediated heart rate variability (vmHRV). Here, we aimed to quantify the current evidence on alterations in resting state vmHRV in individuals with BPD, relative to healthy controls. A rigorous search of the literature, according to the "*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*", revealed 5 studies suitable for meta-analysis, reporting vmHRV in individuals with BPD (n=128), relative to healthy controls (n=143). Short-term measures of resting state vmHRV were extracted and subjected to meta-analysis using both random- and fixed effect models in *RevMan*. BPD displayed lower resting state vmHRV relative to healthy controls in random- (Hedges' g = -0.57, 95%CI [-1.12;-0.01], k=5) and fixed-effect meta-analysis (Hedges' g=-0.54, 95%CI [-0.84;-0.25], k = 5). Control for potential publication bias did not change observed findings. Lowered resting state vagal tone may be an important trait characteristic underlying BPD. As prior studies have observed lowered vmHRV in a variety of psychiatric disorders, we propose that lowered vmHRV may reflect a common psychophysiological mechanism underlying difficulties in emotion regulation and impulsivity, in particular.

Keywords: *borderline personality disorder; vagal tone; heart rate variability; meta-analysis; impulsivity; emotion regulation*

1. Introduction

Borderline Personality Disorder (BPD) is characterized by pathological personality traits in the domains of negative affectivity, emotional liability, anxiousness, separation insecurity or depressivity and behavioural characteristics such as disinhibition, (i.e., impulsivity and risk taking) and antagonism (hostility) (Leichsenring et al., 2011; American Psychiatric Association, 2013). BPD affects about 1-2% (Coid et al., 2006; Trull et al., 2010) of the general population and is the most common personality disorder in clinical settings (American Psychiatric Association, 2001).

Several key features of BPD (i.e., emotional liability and impulsivity) represent impairment in inhibitory control, the capacity to inhibit and regulate prepotent emotional responses. Heart rate variability (HRV) - the variability in the time-series of consecutive heartbeats – is widely perceived as a psychophysiological marker of emotion regulation capacity (Lane et al., 2009; Park and Thayer, 2014) and inhibitory control (Hovland et al., 2012; Pappens et al., 2014; Gillie et al., 2014; Wendt et al., 2015). Parasympathetic modulation of the heart rate is fast (timescale on the order of milliseconds) while sympathetic effects are much slower (Levy, 1997). Therefore, high-frequency (HF) HRV, respiratory sinus arrhythmia (RSA), and time-domain measures reflecting these fast changes (i.e., the time-domain root-mean-square of successive R-R-interval differences, RMSSD measure) provide a readily available, surrogate measure of vagal activity (Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Vagally mediated HRV (vmHRV) is strongly associated with emotion regulation (Thayer et al., 2012) and underpins individual differences in the perception of emotional stimuli (Park et et al. 2013). It predicts affective instability in daily life (Koval et al., 2013) and is inversely correlated to greater reports of difficulties in emotion regulation (Berna et al., 2014; Williams et al., 2015). While emotional dysregulation is a core feature of BPD itself, it may also be an important candidate to explain high rates of comorbidity between BPD and other mental disorders (e.g. substance use disorders, affective disorders) (Dell'Osso et al., 2010).

Furthermore, lower vmHRV has been linked to a variety of other mental and physical health conditions (Kemp and Quintana, 2013), within the psychiatric domain in particular (Malik and Camm, 2007). Reduced vmHRV relative to controls is reported in major depressive disorder (MDD) (Kemp et al., 2010) and MDD with comorbid generalized anxiety disorder (Kemp et al., 2012), as well as MDD with melancholia (Kemp et al., 2014). Reduced vmHRV is also observed in anxiety disorders (Chalmers et al., 2014) such as social anxiety disorder (Alvares et al., 2013), generalized anxiety disorder (Thayer et al., 1996; Friedman and Thayer, 1998a; Thayer et al., 2000), and panic disorder (Friedman and Thayer, 1998b; Cohen et al., 2000). Intriguingly, HRV has also been linked to risk taking behavior (Bhatt et al., 2015) as well as to personality traits (e.g. neuroticism) in the general population (Zohar et al., 2013; Huang et al., 2013; Čukić and Bates, 2014) and interpersonal dysfunction (Hansen et al., 2007).

Given the associations and commonalities of key-features of BPD and vmHRV, vagal tone is a promising target for research into shared mechanisms underlying psychopathological disorders that are sequentially comorbid (Caspi et al., 2014) and manifest as BPD. Here we aimed to review and quantify the current evidence on differences in resting state vagal tone comparing individuals with BPD and healthy controls.

2. Methods

2.1 Literature Search

A systematic search of the literature, according to the "*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*" (PRISMA) statement (Moher et al., 2009) was employed using the *PubMed*, *PsycNET/PsycINFO*, *CINAHL Plus*, and *Web of Science* (WOS) databases (*see* **Appendix A** for search terms and hits by database). Additionally, a hand search (i.e., *Google*, *Google Scholar* and other sources) was performed and reference lists of included studies were checked for additional studies eligible for inclusion. After removing duplicates, abstracts of all articles were screened based on pre-defined inclusion

criteria. Abstracts were included if they reported (i) *an empirical investigation* in (ii) *humans* and (iii) *recorded HRV* (iv) *in BPD*. All titles meeting the inclusion criteria were retrieved and reviewed in full-text. Excluded studies and reasons for exclusion are given in *Figure 1*. Empirical investigations were defined as studies involving active data collection in human subjects. Reviews, meta-analysis, comments, single-case reports, or abstracts from conference proceedings were excluded. The full-text of studies qualifying for inclusion were further reviewed and screened for inclusion eligibility. To be included, studies had to report (i) *any measure of vmHRV* in (ii) *clinical samples of BPD patients* characterized by clinical criteria (e.g. DSM, ICD) and diagnostic procedures, or (iii) individuals *high on borderline personality features*, as assessed by psychometric instruments with high specificity and sensitivity when compared to a validated structured clinical interviews; compared to (iii) *non-BPD healthy controls*.

2.2 Data Extraction

All time- and frequency domain measures reflecting vmHRV were considered for inclusion in the meta-analysis. Where citations reported multiple indices of vmHRV, hierarchical inclusion criteria were implemented to prevent conflation of effect-size estimates: HF power was selected for analysis if available, followed by RSA and RMSSD. Authors who reported vmHRV but who did not provide sufficient quantitative data (e.g., only a graphical display) were contacted in order to request the necessary information to derive effect size estimates and confidence limits on the selected indices. When only the standard error of the mean (*SEM*) was reported, the *SD* was calculated by multiplying the *SEM* by the square root of the sample size (Higging and Green, 2011). When descriptive statistics were reported other than the mean, SD or SEM, data were imputed by established procedures where possible (Wiebe et al., 2006; Glass et al., 1981). Studies that reported more than two groups of participants (e.g. BPD vs. generalized anxiety disorder vs. healthy controls) were included as long as findings were available from at least one BPD group against healthy controls, while studies that compared different groups of BPD

patients only were excluded. When multiple groups of BPD patients (e.g., BPD with and without avoidant personality disorder) were reported, each group was compared to the same group of healthy controls.

Descriptive statistics (mean and SD) of vmHRV indices derived from resting baseline recordings were extracted. Where longitudinal or pre-post data were reported, only baseline resting HRV was included to minimize confounding effects by experimental manipulation and conflation of effect size estimates. If long-term (e.g. 24 hours) recordings were obtained, measures from these recordings were included in the analysis. However, it is noted that guidelines for the measurement of HRV suggest "*because of the important differences in the interpretation of the results, the spectral analyses of short- and long-term electrocardiograms should always be strictly distinguished*" (Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Thus, meta-analysis for short- and long-term recordings was done separately when sufficient data was available for analysis.

2.3.2 Fixed Effect Estimation and Heterogeneity

True effect estimates were computed as adjusted standardized mean differences (Hedge's g). Meta-analyses was performed using both fixed-effect (FE) and random-effects (RE) models. When results of both analyses were consistent (with confidence intervals (CI) of fixed-effect analyses being included within that of the random-effects analysis), the results from random-effects models are reported and graphically displayed, as it better conveys the variability of data (Higging and Green, 2011). Possible sources of heterogeneity or inconsistency among trials in the magnitude or direction of effects were investigated. Bias was examined using a funnel plot of effect size against standard error for asymmetry and heterogeneity was assessed using the standard I^2 index, Chi-Square, and Tau^2 tests (Higgins and Thompson, 2002). Substantial heterogeneity was assumed if I^2 was greater than 50%, indicating that 50% of the variability in the outcome cannot be explained by sampling variation. Meta-analytic computations

were performed using RevMan (*Version 5.3.4, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014*).

3. Results

3.1 Study Selection

Based on the screening of full-texts, one study conducted in para-suicidal girls with no distinct assessment of BPD features (Crowell et al., 2005) and one study on heroin dependent men with BPD characteristics (Hunag et al., 2012) were excluded. One study assessing BPD symptoms in healthy participants but reporting only correlational results and no group comparisons was excluded (Sylvers et al., 2008). Two studies were excluded (Dixon-Gordon et al., 2013; Ebner-Priemer et al., 2008), because they reported an overlapping sample of studies published earlier (Dixon-Gordon et al., 2011; Ebner-Priemer et al., 2007). Of these earlier studies one was finally included (Dixon-Gordon et al., 2011). The other study (Ebner-Priemer et al., 2007) was excluded, because it was the only study reporting long-term (24 hour) recording of HRV (insufficient data for comparisons in the meta-analysis). Two studies published in 2014 and 2015 were excluded (Fitzpatrick and Kuo, 2014; Kuo et al., 2014), because they reported data from the same sample of a previously published report (Kuo and Linehan, 2009) that was included. One study was excluded (Svaldi et al., 2012) because it did not include a group of healthy controls. Another study was excluded because it didn't report a measure of vmHRV (Battaglia et al., 1995). Following exclusions, a total of 5 studies (Austin et al., 2007; Kuo and Linehan, 2009; Weinberg et al., 2009; Dixon-Gordon et al., 2011; Gratz et al., 2013) were eligible for inclusion in the meta-analysis. These studies are summarized in *Table 1*.

3.2 Summaries of Included Studies

Austin et al. (2007) measured RSA during viewing of three 10 min film clips, in 9 female patients with BPD, who were off medication while participating in the study, and in 11 female controls, free of psychiatric or neurological disorders. The first and third film clips were selected as clips that would elicit

a strong emotional response; the second clip was a neutral scene. The authors reported a significant group effect for RSA across all conditions. RSA was similar for the two groups during baseline. While over the course of the experiment, RSA increased in controls it decreased in BPD (Austin et al., 2007). The authors concluded that the BPD group had poor vagal regulation in comparison with healthy controls. 5 minute resting baseline data was extracted and subjected to meta-analysis.

The study by Gratz et al. [2013] was conducted in 57 women (39 with BPD, 18 controls) measuring resting baseline and phasic HF-HRV during a distress-tolerance task. While controls showed high rates of lifetime psychiatric disorders, participants in both groups with current (past two weeks) manic, hypomanic, or depressive mood episodes, current (past-month) substance dependence, and/or primary psychosis were excluded from the study. Furthermore, participants were excluded for current use of psychotropic medications other than antidepressants, including benzodiazepines, beta-blockers, and mood stabilizers. Women with BPD were divided into two groups: those with comorbid avoidant personality disorder (AVPD), and those without comorbid AVPD. The authors found no significant group differences comparing BPD with AVPD, BPD without AVPD, and controls on HF HRV at baseline and HRV during the low-stress section of the distress tolerance task - causing them to conclude that without emotional distress, BPD participants respond similarly to normal controls (Gratz et al., 2013), based on a significant difference during a stress task. The authors reported that while BPD patients without AVPD and controls displayed a slight increase in HF-HRV, BPD patients with AVPD displayed a decrease in HF-HRV reactivity (Gratz et al., 2013). 5 minute resting baseline data was extracted and subjected to meta-analysis.

Kuo and Linehan (2009) investigated RSA in 20 women with BPD, 20 women with social anxiety disorder (SAD), and in 20 women with no current Axis I disorders or BPD. Participants with schizophrenia, schizophreniform, schizoaffective disorders, psychosis nonspecified, bipolar disorder, current substance dependence, epilepsy or seizure disorder, heart disease, and asthma were excluded. Furthermore, participants taking any psychotropic medication other than selective serotonin reuptake

inhibitors (SSRIs), major tranquilizers, antihistamies, or beta-blockers were excluded. BPD was determined by the Structured Clinical Interview for Axis I DSM-IV Axis II Personality Disorders (SCID-II) and RSA was measured via ECG. The study consisted of two sessions (in counterbalanced order), one in which there were baseline (true and vanilla baseline each 4 minutes) recordings followed by standardized emotion induction (*sad*, *fear*, *anger*, *neutral*). The other session comprised baseline recordings followed by emotion induction using personally relevant content. True baselines and vanilla baselines were each combined across the films and imagery conditions. The authors found that the BPD group exhibited reduced baseline RSA compared with controls and SAD patients. After investigating interactions between group status and phase of the study, the only significant difference was found between BPD and SAD patients during the sad emotion induction, with BPD subjects displaying a significant increase in RSA from baseline to the sad film while the SAD subjects displayed a non-significant decrease in RSA (Kuo and Linehan, 2009). Data from true and vanilla baseline epochs (30 seconds each) were extracted and subjected to meta-analysis. During the vanilla baseline, participants engaged in a non-stressful, non-demanding cognitive task requiring them to count the number of times a specified color appeared on a screen (Kuo and Linehan, 2009).

The study by Weinberg et al. [2009] investigated RSA and Cardiac Sympathetic Index (CSI, a measure of sympathetic activity) in twelve non-clinical participants with BPD and 28 controls without BPD. Participants in the BPD group screened positive for BPD in the McLean Screening Instrument for BPD (MSI-BPD), which shows good sensitivity and specificity (above .90) when compared to a validated structured interview (Zanarini et al., 2003). The authors did not control for medication status of the participants. Participants completed a baseline-resting period, followed by a mental arithmetic task. The authors reported a main effect of gender on RSA, such that females displayed lower parasympathetic activity than males. For CSI there was also a main effect of gender, with female participants displaying higher sympathetic activity (Weinberg et al., 2009). There was no effect of gender on mean HR. In regards to parasympathetic activation, the authors reported a main effect for group, with BPD participants

displaying lower overall parasympathetic activity compared to controls. This effect was robust to inclusion of gender as a covariate. They did not find an interaction between stressor and group. For CSI, the authors reported a main effect for group, with BPD subjects displaying more sympathetic activity than controls (Weinberg et al., 2009). They also found an interaction between the stressor and group such that CSI increased during the stressor for the BPD subjects, but decreased for the control group during the same time period. This interaction remained when gender was included as a covariate. Lastly, they found no effect of group on HR, nor did they find an interaction between group and stage for HR. 5 minute resting baseline data were extracted and subjected to meta-analysis.

Dixon-Gordon et al. [(2011) recruited 87 female university students and assessed BPD through the Personality Assessment Inventory—Borderline Features Scale (PAI–BOR (Morey, 1991)). The authors assessed cardiac health using a brief structured interview, although they did not asses the medication status of the participants. Participants were divided into low borderline personality (BP) (n = 29), mid BP (n = 32), and high BP features (n = 26) groups. For the present meta-analysis, we compared the high and low BP feature group. The authors created a high BP feature group on the basis of a cut-off value for the PAI-BOR, which has a high predictive power (positive of .97) for a BPD diagnosis according to the Structured Clinical Interview for DSM–IV Personality Disorders (Morey, 1991). Participants completed a 5-minute true baseline, vanilla baseline, responded to three randomly selected Means–ends problem-solving test procedures (MEPS) scenarios, completed a second vanilla baseline, underwent the negative emotion induction procedure, responded to three randomly selected and randomly ordered MEPS scenarios, and completed a final true baseline, each 5 minutes in length. HRV was measured continuously throughout the procedures. The authors found no significant Group x Condition effect on RSA (Dixon-Gordon et al., 2011). 5 minute resting baseline data were extracted and subjected to meta-analysis.

3.3 Meta-Analysis

Among the different measures of HRV reflecting vagal activity, only RSA and HF-HRV were reported by multiple studies (*Table 1*) and subjected to meta-analysis. For studies reporting multiple comparisons (Kuo and Linehan, 2009; Gratz et al., 2013) data were first combined across sub-groups to yield a summary effect (Borenstein et al., 2009) (sub-group values reported in *Figure 2*). The study by Kuo & Linehan (2009) reported the SEM instead of the SD and transformations were applied before analysis. Weinberg et al. (2009) and Dixon-Gordon et al. (2011) provided additional data on which meta-analysis was conducted here.

Effect sizes of all included studies are presented in *Figure 2*. FE meta-analysis across all included studies (n=5) and available comparisons (k=7) revealed a significant (Z=4.60, *p<.0001*) main effect (Hedge's g=-0.59, 95%CI [-0.84;-0.34]), indicating lower vagal activity indexed by HF-HRV/RSA in BPD patients (n=128) compared to healthy controls (n=143) (*Figure 2*). RE meta-analysis showed similar results and a significant main effect (Z=2.74, *p=.006*; Hedge's g = -0.61, 95%CI [-1.04;-0.17], k=7), as illustrated in *Figure 2*. Significant heterogeneity was observed (*see* test results in *Figure 2*), and visual examination of the funnel plot (*Figure 3*) revealed asymmetry, caused by one outlier (Gratz et al., 2013; BPD without comorbid AVPD group) indicating publication bias.

Subsequently, we excluded studies from RE meta-analysis, to avoid having some participants contributing information to more than one effect size. The studies reporting only a single comparison (n=3) (Austin et al., 2007; Weinberg et al., 2009; Dixon-Gordon et al., 2011) in BPD (n = 49) and healthy controls (n=67) were set as starting point (Z=2.74, *p=.006*, Hedges' g=-0.68, 95%CI [-1.17;-0.19], k=3). Next, the study by Kuo and Linehan (2009) was added to the analysis (BPD n=69; controls=87). Including either the *vanilla baseline* (Z=3.77, *p=.0002*, Hedges' g=-0.80, 95%CI [-1.22;-0.39], k = 4) or the *true baseline* (Z=3.80, *p=.0001*, Hedges' g=-0.80, 95%CI [-1.21;-0.39], k=4), did not result in differential effects.

We decided to proceed with the *vanilla baseline* condition, given that it resulted in a slightly smaller effect, indicated by the Z score, to provide a more conservative estimate of the true effect. Both studies by Gratz et al. (2013) were included, given the non-overlap in the group of BPD patients with (n=13) and without AVPD (n=26). The final main effect remained robust and significant in RE (Z=2.16, *p=.03*, Hedges' g=-0.52, 95%CI [-0.98;-0.05], k=6) and FE (Z=3.61, *p=.0003*, Hedges' g=-0.50, 95%CI [-0.77;-0.23], k=6) models, comparing BPD (n=108) and healthy controls (n=123). Removing the previously identified outlier (*Figure 3*) from analysis, caused an increase in the effect size estimate derived from RE (Z=3.55, *p<.001*, Hedges' g=-0.70, 95%CI [-1.08;-0.31], k=5) and FE (Z=4.51, *p<.001*, Hedges' g=-0.70, 95%CI [-1.00;-0.40], k=5) models (BPD n=82; controls=105). On the other hand, excluding the BPD group with comorbid AVPD (BPD n=95; controls=105) - to avoid introducing error by including a BPD group with a comorbid psychiatric condition - also yielded significant effect estimates in RE (Z=1.99, *p=.005*, Hedges' g=-0.57, 95%CI [-1.12;-0.01], k=5) and FE (Z=3.61, *p=.0003*, Hedges' g=-0.54, 95%CI [-0.84;-0.25], k=5) models (*Figure 4*).

4. Discussion

The present meta-analysis aimed to summarize differences on resting vagal tone, indexed by vmHRV, comparing patients with BPD (n=128) and healthy controls (n=143). Meta-analyses on all included studies and sub-group comparisons, revealed significant and sizeable main effects using either FE or RE models (g=-0.50 to -0.70), indicating decreased vagal tone during resting state in BPD patients (*Figure 2*).

Of the included studies, only two initially reported statistically significant differences between BPD patients and controls (Kuo and Linehan, 2009; Weinberg et al., 2009), highlighting the utility of meta-analysis over individual studies which often lack statistical power. Thus, while the number of studies we included in analysis is small, it is still a valid approach to draw more objective conclusions from a

body of contradictory evidence. The study by Austin et al. (2007) reported reduced RSA in BPD patients, although statistical tests did not reach the set level of significance. It is instructive to note that this study investigated a relatively small sample of 9 BPD patients and 11 healthy controls. The study by Gratz et al. (2013) reported no significant differences between groups (BPD-AVPD; BPD+AVPD, healthy controls) on baseline HF-HRV. BPD patients without comorbid AVPD even displayed slightly increased HF-HRV at baseline compared to controls, although these findings were not significant. However, in addition to baseline HF-HRV, the authors also reported *Acclimation HF-HRV* (Gratz et al., 2013, *Table 1*), which according to the authors, refers to the low-stress levels of the PASAT-C [*Personal Communication*], that – in line with the present findings – shows a linear trend such that BPD patients with comorbid AVPD display the lowest HF-HRV, followed by BPD patients without comorbid AVPD, and healthy controls, the group displaying the highest HF-HRV. The study published by Dixon-Gordon and colleagues (2011) didn't obtain significant group differences, but a graphical display of baseline RSA values (Dixon-Gordon et al. 2011, *Figure 1*) was displayed that is consistent with the findings we present here. A linear trend is displayed, such that individuals high on BP features display the lowest RSA, followed by those with moderate BP features, relative to participants low on BP features who displayed the greatest levels of RSA (Dixon-Gordon et al. 2011).

One study (Ebner-Priemer et al., 2007) excluded from analysis partially contradicts the findings we report here. This study was excluded because it was the only study that reported vmHRV derived from long-term recordings. Ebner-Primer et al. (2007), found *lower* 24-hour HF-HRV compared to controls in the entire sample of BPD patients and those whom were medicated, but *greater* 24h HF-HRV in non-medicated BPD participants. The authors discuss the potential impact of respiration (which was not controlled for) and a simultaneous up-regulation of sympathetic and parasympathetic activity to explain their findings (Ebner-Priemer et al., 2007). Guidelines for the measurement of HRV indicate that spectral analysis of 24-hour HRV (where spectral estimates are calculated over long data epochs) may not reflect autonomic modulation accurately, and that modulation is better captured by estimates based on shorter

data epochs (Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). However, the findings by Ebner-Primer et al. (2007) do raise the concern of medication effects on vmHRV. Given the significant differences on HRV between medicated and non-medicated BPD patients in this study (Ebner-Priemer et al., 2007), medication intake needs to be considered as an important covariate.

Anti-hypertensives, antidepressants (Kemp et al., 2011, 214), analgesics (Koenig et al., 2015) and other anti-cholinergics can have a significant impact on vmHRV, and as highlighted by Ebner-Primer et al. (2007) controlling for medication intake may yield different findings. However, the participants in the study by Austin et al. (2007), were off medication at the time of the study. Participants in the study by Gratz et al. (2013) were excluded for the current use of psychotropic medications other than antidepressants and the authors found no significant differences, when controlling for psychotropic medication status. In the study by Kuo and Linehan (2009), 4 of the BPD participants were on selective serotonin reuptake inhibitors (SSRIs) and those were not controlled for in statistical analysis. The study by Weinberg et al. (2009) didn't report medication intake, but their sample was drawn from a screening completed by college students - at least minimizing the likelihood that a fair amount of participants was on psychotropic medication at the time of assessment. The study by Dixon-Gordon et al. (2011) did not control for medication status of the participants, but assessed cardiac health using a brief structured interview.

Most medicated patients in the included studies were on SSRIs that typically lead to small decreases in HRV (Kemp et al., 2011, 214). Thus, while the effect shown is unlikely to be the consequence of medication only, intake of SSRIs – that are frequently prescribed in clinical BPD (Rinne et al., 2002) - might further decrease vagal activity. However, based on the present data we were not able to run meta-regression on the confounding effect of medication, given the heterogeneity of included samples or insufficient reporting of medication status in the included studies.

Another issue concerning the assessment of resting state vagal tone by measures of vmHRV is the trait specificity that can increase under well-controlled recording conditions (i.e., when breathing is controlled for) (Bertsch et al., 2012). It is well known, that respiration has a greater effect on RSA (assessed using the peak-to-trough method) and HF-HRV than on RMSSD. Our group (Hill and Siebenbrock, 2009) as well others have shown that RMSSD is less affected by respiration than other indices of HRV including spectrally derived HF-HRV (Penttilä et al., 2001). HRV indices derived from frequency domain analysis provide information of different quality and detail compared to time domain analysis (Sinnreich et al., 1998). While RMSSD and HF are highly correlated (Goedhart et al., 2007), it has been suggested that time domain parameters can be estimated with less bias and considerably smaller variability as compared with frequency domain parameters (Kuss et al., 2008). To our surprise, none of the studies on vmHRV in BPD reported time-domain measures of HRV. Except for the study by Gratz et al. (2013) – which reported HF-HRV – all of the included studies reported RSA, and none of the studies controlled breathing during the recording of vmHRV. Given that RSA is the index of vmHRV most likely to be affected by respiration, future studies would do well to use other indices of vmHRV less affected by respiration or at least to record, and possibly control for, respiration.

In addition to medication intake and breathing frequency, co-morbid psychiatric conditions and overall physical health (Kemp & Quintana, 2013) and well-being (Jarczok et al., 2015) might serve as important covariates. Austin et al. (2007) report that BPD patients were screened to eliminate comorbid conditions, but provide no further information. While Gratz et al. (2013) excluded BPD patients and controls with current manic, hypomanic, or depressive mood episodes or current substance dependence, and/or primary psychosis, 75% of participants in the control group met the criteria for at least one lifetime psychiatric disorder. In the study by Kuo and Linehan (2009), the majority of the BPD participants had multiple comorbid diagnoses. Again, the study by Weinberg et al. (2009) didn't control for comorbid conditions, given the nature of the sample. For the sake of completeness, Ebner-Primer et al. (2007) excluded participants with a lifetime history of schizophrenia, bipolar disorder, or current alcohol/drug

abuse. However, the majority of BPD patients had comorbid psychiatric conditions such as current MDD (36%), current anxiety disorders without posttraumatic stress disorder (PTSD; 60%), current PTSD (60%), or a lifetime history of eating disorders (50%) or substance abuse (60%) (Ebner-Primer et al., 2007). Psychiatric comorbidity is expected in patients with BPD; thus recruitment of *pure* BPD samples in future studies is unlikely. BPD is associated with particularly high rates of mood and anxiety disorders that have been shown to be associated with reduced vmHRV (see *Introduction*).

Furthermore, lower vmHRV is related to poor physical health (Kemp & Quintana, 2013) and it has been shown that BPD is related to both chronic medical illness as well as poor health-related lifestyle choices (Frankenburg and Zanarini, 2004; Keuroghlian et al., 2013). As a future direction, research needs larger samples to carefully control for these comorbid psychiatric and somatic conditions.. While we consider lower resting state vagal tone to represent a common non-specific physiological mechanism associated with general psychopathology (Caspi et al., 2014) and poor physical health (Kemp & Quintana, 2013) the relative variance explained by BPD versus comorbid conditions, remains to be revealed. Likewise, future research is needed to address whether certain symptom dimensions underlying BPD (i.e., affective dysregulation, impulsive-behavioral dyscontrol, and cognitive-perceptual symptoms) are in particular related to lower resting state vmHRV, and may explain the high overlap of findings in BPD and diverse comorbid disorders. While existing data is supportive of a strong relationship of vmHRV with emotion dysregulation (Lane et al., 2009; Thayer et al., 2012; Park and Thayer, 2014), future studies including a thorough assessment of BPD related symptom dimensions are necessarily to address its potential association with impulsive-behavioral dyscontrol and cognitive-perceptual symptoms in BPD.

There is some evidence supporting idea that lower vmHRV might precede the development of BPD. Research on the genetic and environmental influences on human HRV has shown that genetic factors account for between 13% to 57% (Singh et al., 1999; Uusitalo et al., 2007) of the variation among HRV measures in adults, and there is good evidence for genetic contributions to HRV in children (Mueller

et al., 2012). Furthermore, important heritable traits such as affective instability are related to HRV (Koval et al., 2013), such that individuals with lower parasympathetic tone are emotionally less stable.

We recently demonstrated that women with a past, but not current, anxiety disorder, as well as their offspring display reductions in HRV (Braeken et al., 2013). Offspring of mothers with a past anxiety disorder also displayed increased fearfulness in this study. It has also been shown, that children of mothers with a history of childhood physical and emotional abuse have lower vmHRV (Jovanovic et al., 2011).

On the other side, research has shown that the recent experience of persistent emotional stress, influences vagal modulation of the heart, regardless of trait anxiety (Dishman et al., 2000). Consistent with recent findings on how the early caregiving environment shapes the stress response system reactivity in humans(McLaughlin et al. 2015). Given that experiences of childhood abuse and neglect are uniquely associated with BPD feature severity (Kuo et al., 2015; Infurna et al., 2014) such maltreatment might overstrain early adaptive emotion regulation capacities, during the sensitive period of childhood, and finally may constitute a developmental pathway to BPD (McLaughlin et al. 2015). Reduced adaptive capacities - indexed by lower resting vmHRV – might represent a predisposition (trans-generational perspective) that is further burdened by early life experience within the childhood environment (Braeken et al., 2013).

Generally speaking, it has been shown that peer problems, anger, anxiety and sadness are associated with lower vmHRV in children (Michels et al., 2013), with important implications for adaptive emotion regulation. Active emotion regulation (suppressing or reappraising) is associated with acute increases in vmHRV (Butler et al., 2006). However, such response is not observed in PTSD patients who "*experience […] a degree of autonomic hyperactivation at rest, […] [leaving them] unable to marshal a further stress response to the recounting of the triggering trauma, as compared to control subjects*" (Cohen et al., 1998). Whereas these findings have been replicated in traumatized preschool children with and without PTSD (Scheeringa et al., 2004), we have recently shown that the control over memory retrieval (Gillie et al., 2014), the inhibition of conditioned fear (Wendt et al., 2015), and safety learning

(Pappens et al., 2014) – all associated with resting state vmHRV – might present important mechanistic processes, linking vagal tone and early life adversity to the development of psychopathology.

On the level of the central nervous system, we can speculate on several mechanisms and neural mediators underlying the relationship between HRV and BPD. Both the amygdala and the ventromedial prefrontal cortex (PFC) are significantly associated with HRV across neuroimaging studies using cognitive and emotional tasks (Thayer et al., 2012). There is good evidence, that the capacity of the PFC to exert inhibitory control over subcortical brain structures may be indexed with vmHRV at rest (Ahern et al., 2001; Thayer et al., 2009), since increased activity of the PFC leads to decreased heart rate and increased HRV via multiple pathways (Thayer et al., 2009). The PFC is involved in regulatory and adaptive behaviors (Miller and Cohen, 2001), and related to impulsivity (Kim and Lee, 2011) and emotion regulation (Banks et al., 2007), which are both well known as characteristic features of BPD (APA, 2013).

Individuals with BPD show hypometabolism of glucose in the PFC and limbic system relative to controls, that "could parallel impaired serotoninergic function and be therefore related to […] impulsiveness" in BPD (De La Fuente et al., 1997). Other studies provided evidence for abnormal prefrontal cortical modulation of increased activity in the amygdala in response to aversive emotional stimuli in BPD (Herpertz et al., 2001). Studies on PFC-amygdala connectivity found coupling of metabolic activity between the right orbitofrontal cortex and ventral amygdala in healthy subjects but not in impulsive aggressive BPD patients (New et al., 2007). In line with this, it has been shown, that limbic dysregulation is associated with lower HRV and increased trait anxiety (Mujica-Parodi et al., 2009). Limbic dysregulation by the PFC might therefore be an important neural mechanism underpinning of lower resting state HRV in patients with BPD.

We envisage several potential directions for future research. Importantly, all studies included in this meta-analysis were carried out in adult patients of 18 years and older. However, BPD usually emerges during adolescence and continues into adulthood (Kaess et al., 2014). Thus, cross-sectional studies in younger BPD samples and longitudinal studies to explore the temporal and causal associations between

vagal activity and BPD are of great interest. Furthermore, low resting state vagal tone can be conceptualized as an endophenotype for the development of various psychiatric disorders (Clamor et al., 2015). Thus, studies exploring developmental pathways of BPD in younger patients are of high relevance and would have great importance.

Furthermore, an important missing piece in this puzzle are studies to determine whether established treatment options for BPD favorably impact on HRV; it is possible, for instance, that vagal dysfunction is reversible by effective (psychotherapeutic) treatment. Recently, we examined such dynamics of abnormalities in cardiac vagal control over time in depressed patients treated with sertraline and healthy volunteers enrolled in a 12-week protocol (Schafer et al., 2015). Neural activity and vagal control were measured for all subjects at 0, 2, 6 and 12 weeks using fMRI imaging and synchronized electrocardiographic (ECG) recordings. Sertraline treatment led to significant increase in brain-HRV co-variation for patients compared to controls. In BPD, psychotherapy is the primary treatment option, complemented by symptom-targeted pharmacotherapy (Leichsenring et al., 2011). Studies extending the current findings and exploring the impact of available treatment options on resting state vmHRV, as well as the potential to monitor therapeutic outcome through the assessment of vmHRV, are an interesting field for future research. Improved emotion regulation capacity after successful therapeutic treatment in BPD might be further reflected by increased cardiac vagal tone during the resting state. On the other hand, potential treatment options designed to increase resting vagal tone might themselves lead to improved emotion regulation capacities in individuals with BPD. It is well known, that physical activity can increase vmHRV (Rennie et al., 2003; Buchheit et al., 2007) and recently we have shown that changes in diet and nutrition can increase resting vmHRV and lead to a reduction of anxiety (Hansen et al., 2014). Furthermore, research on direct vagus nerve stimulation has suggested antidepressant effects in treatment-resistant depression (Bajbouj et al., 2010; Goodnick et al., 2001). Vagus nerve stimulation in other psychiatric disease such as BPD is an interesting direction for future research.

Finally, of the included studies only Weinberg et al. recruited a mixed sample of female and male participants (Gratz et al., 2013). They report a main effect of gender on RSA such that female participants exhibited significantly lower parasympathetic activity overall than males – contradicting current findings on sex differences in HRV (Koenig and Thayer, *under review*). Research has yet to explore, in detail, the implications of sex differences in HRV for psychiatric research. While low cardiac vagal control is linked to depression and anxiety, the prevalence of depressive (Piccinelli and Wilkinson, 2000) and anxiety disorders (McLean et al., 2011) is higher in females than in males. We've previously suggested that sex differences in the attention to emotion, and subsequent emotion regulation strategies, might explain sex differences in depression (Thayer et al., 2003). Such compensatory mechanisms might account for the higher prevalence for emotion disorders in females, despite greater cardiac vagal tone. While the prevalence of lifetime borderline personality disorder is similar among men and women (American Psychiatric Association, 2013), research on vmHRV in males with borderline personality disorder is rare.

Conclusion

This is the first meta-analysis to quantify differences in resting state vagal tone, indexed by vmHRV comparing clinical BPD patients or individuals with characteristic features of BPD and healthy controls. Lower resting state vagal tone – a finding associated with moderate effect size – might be an important trait characteristic underlying BPD, providing a psychophysiological mechanism underlying difficulties in emotion regulation and impulsivity in those with BPD. Research has yet to investigate younger samples of BPD patients to explore if decreased vagal tone represents an endophenotype preceding the development of BPD or instead, whether it is the consequence of the disorder. Future studies need to improve by carefully control for the effect of psychotropic medication and comorbid psychopathology.

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**: indicates that the study was included in the meta-analysis*

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Appendix A: Search strategy by database

PubMed [search strategy: (borderline personality) AND ((heart rate variability) OR respiratory sinus arrhythmia)];

PsycNET/PsycINFO [search strategy: (Any Field: (borderline personality)) AND (Any Field: (heart rate variability) OR Any Field: (respiratory sinus arrhythmia))];

CINAHL Plus [search strategy: (Any Field: (borderline personality)) AND (Any Field: (heart rate variability) OR Any Field: (respiratory sinus arrhythmia))];

Web of Science [search strategy: (Topic:(borderline personality)) AND (Topic: (heart rate variability) OR Topic: (respiratory sinus arrhythmia)) Timespan: All years; Search language=Auto].

Figure Captions

Figure 1: PRISMA Flow-Chart

Figure 2: Forrest Plot of all Included Studies Reporting HF-HRV/RSA by Sub-Group Analysis; *green shaded values were imputed from missing data; violet shaded values were provided by the authors*

Figure 3: Funnel-Plot; *Note: the outlier on the far right side refers to BPD without comorbid AVPD group reported by Gratz et al.* [48]. *Removing the outlier significantly increased the effect estimate derived from FE and RE meta-analysis.*

Figure 4: Forrest-Plot – Conservative Estimate of the True Effect; ***Note:*** *the group of BPD patients with comorbid AVPD reported by Gratz et al.* [49] *and the "true baseline" condition reported by Kuo & Linehan* [44] *were excluded from this analysis.*