

BORDERLINE PERSONALITY DISORDER, CO-OCCURRING SUBSTANCE USE,
AND AUTONOMIC DYSREGULATION

by

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ABSTRACT OF THE DISSERTATION

Borderline Personality Disorder, Co-occurring Substance Use,
and Autonomic Dysregulation

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Borderline personality disorder (BPD) is a complex disorder characterized by intense and rapidly shifting affective states, instability in self-image, chronic feelings of emptiness, and dissociation. Individuals with BPD commonly engage in substance use, and self-injurious and suicidal behaviors as a way to manage intolerable affect. To date, the cognitive components of emotion dysregulation in BPD have received much research attention. The collateral psychophysiological processes, however, remain poorly understood. Because emotion regulation is mediated by both cognitive and physiological processes, this knowledge gap may be limiting progress in the treatment of BPD. Thus, this investigation sought to comprehensively assess psychophysiological differences between individuals with BPD and healthy controls, and examine whether a loss of flexibility in fundamental autonomic nervous system (ANS) processes may contribute to the emotion dysregulation observed in BPD. Psychophysiological differences between individuals with BPD and healthy controls were assessed at rest, during exposure to emotionally evocative images selected from the International Affective Picture System (IAPS), and during a post cue exposure recovery period, with additional tests for the effects of dissociative tendencies on

cue reactivity, and substance use on cue exposure recovery. Indices of heart rate variability (HRV), electrocardiogram (ECG) derived measures of neurocardiac signaling, as well as continuously recorded blood pressure (BP) and skin conductance (SC) were used to operationalize modulation of psychophysiological arousal. At baseline, the BPD group showed significantly higher heart rate (HR) and greater skin conductance variance (SCV) compared to the control group, but were similar on measures of HRV and blood pressure variability (BPV). Across tasks, there were significant main effects of group and time (cue reactivity and cue recovery) on HR and SCV, and a main effect of time for HRV. However, no interaction effects were observed, suggesting groups were not different in how they responded to or recovered from exposure to emotionally evocative stimuli. This was in spite of the fact that participants with BPD rated the images as subjectively more arousing than controls. Notably though, a posteriori analyses found that BPD severity moderated psychophysiological response to, as well as recovery from, exposure to emotionally evocative images. In addition, analyses for the effects of trait dissociative tendencies on cue reactivity showed trait dissociation moderated change in HRV and BPV from baseline to cue exposure. Analyses for the effects of substance use on cue exposure recovery, however, were limited by unanticipated low levels of past month and past year substance use within the BPD group, though past month alcohol use negatively impacted systolic arterial blood pressure variability during recovery from exposure to emotionally evocative images. Results are discussed within the context of polyvagal theory and future research directions are considered.

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Introduction

Borderline personality disorder (BPD) is a complex disorder characterized by intense and rapidly shifting affective states, impulsivity, and instability in self-image (Bender & Skodol, 2007; Koenigsberg et al., 2002; Links, Heslegrave, & van Reekum, 1999). Individuals with BPD commonly report feelings of profound emptiness, shame, loneliness, panic, and rage, and are particularly sensitive to feelings of rejection, isolation, and perceived failure (Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004; Linehan, 1993; Rizvi, Brown, Bohus, & Linehan, 2011). This pervading constellation of aberrant states often manifests in an intense fear of abandonment, self-injurious and suicidal behaviors, and in some instances, psychotic symptoms (Rizvi & Salters-Pedneault, 2013; M. Z. Rosenthal et al., 2008).

Because BPD symptomology makes it difficult to respond appropriately to stressors, persons with this disorder tend to experience a wide variety of social challenges, including difficulties maintaining close relationships and employment, and poor academic performance (Austin, Riniolo, & Porges, 2007). To complicate matters further, BPD is highly comorbid with other conditions associated with problems of affect regulation, including anxiety disorders (Grant et al., 2008). Further, many individuals with BPD turn to alcohol and other drugs in an effort to self-regulate highly labile emotion and aversive mood states (Trull, Sher, Minks-Brown, Durbin, & Burr, 2000). As such, substance use disorders are also highly comorbid with BPD, and may play a role in maintaining BPD symptomology, complicate treatment outcomes, and exacerbate already strained

interpersonal relations (Axelrod, Perepletchikova, Holtzman, & Sinha, 2011; Dimeff, Rizvi, Brown, & Linehan, 2000; Kruegelbach, McCormick, Schulz, & Grueneich, 1993).

While the cognitive components of emotion dysregulation in BPD have received much research attention, the collateral psychophysiological processes remain poorly understood. This gap may be limiting progress in the treatment of BPD because emotion regulation is mediated by both cognitive and physiological processes supported by the central autonomic network (CAN; Benarroch, 1997), a brain system that integrates cerebral and limbic neural signaling, and modulates physiological activity and reactivity (Benarroch, 1997; Hagemann, Waldstein, & Thayer, 2003; Thayer & Lane, 2000, 2009).

Central autonomic network control of physiological processes via the autonomic nervous system (ANS) reflects an important component of integrated brain-body communication that supports adaptability to changing environmental and internal demands (Damasio, 2001; Thayer, Hansen, Saus-Rose, & Johnsen, 2009). Autonomic rigidity impairs the capacity to generate and alter physiological responses in synchrony with emotional or environmental challenges (Appelhans & Luecken, 2006), and may result in emotional arousal being maintained longer than is optimal, leading to negative psychosocial consequences (McEwen & Gianaros, 2010). Substance use may further undermine such processes (Bates, Bowden, & Barry, 2002; Bates & Buckman, 2013; Eddie, 2012). The broad goal of the present study, therefore, was to examine whether a loss of flexibility in fundamental ANS processes may contribute to the symptomology observed in BPD (Stiglmayr et al., 2005), and to investigate the effects of co-occurring substance use.

Because the CAN effects adaptability to environmental and internal demands primarily through its modulation of the cardiovascular system, indices of neurocardiac processes provide informative, objective, and reliable measures of dynamic emotion regulation processes (Hagemann et al., 2003; Task Force, 1996; Thayer & Lane, 2009). Heart rate variability (HRV), variability in R-spike to R-spike intervals in the electrocardiogram (ECG) signal, reflects fine-grained, moment-to-moment changes initiated by the CAN in response to interoceptive and environmental stimuli. Similarly, heart rate (HR), blood pressure (BP), blood pressure variability (BPV), and skin conductance variance (SCV) reflect shifts in autonomic balance between the sympathetic and parasympathetic branches of the ANS. As such, these measures form critical markers of neurovisceral integration and an individual's ability to self-regulate affect (Appelhans & Luecken, 2006; Kemp & Quintana, 2013; Thayer et al., 2009).

The present investigation thus had the following aims: 1) To assess psychophysiological differences between individuals with BPD and healthy controls at rest, 2) to assess psychophysiological differences between individuals with BPD and healthy controls during exposure to International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2005) pictures selected by expert consensus to be evocative to individuals with BPD (Sloan et al., 2010), 3) to assess psychophysiological differences between individuals with BPD and healthy controls during a post cue exposure recovery period, and 4) to investigate the effects of co-occurring substance use on psychophysiological processes in individuals with BPD during the post cue exposure recovery period.

Borderline Personality Disorder – Theoretical Perspectives

Through the years, a number of theories have attempted to explain BPD's etiology and expression. Early psychoanalytic theory (e.g., Kernberg, 1967; Meissner, 1978; Settlege, 1977) considered BPD pathology to lie on the 'borderline' of neurotic and psychotic personality organization, arising from childhood experiences with unempathic, unavailable, or abusive parents who failed to help their children self-regulate emotion. As a result, children who eventually go on to develop BPD were believed to form representations characterized by withdrawal or attack in response to their legitimate expressions of needs and affects. They subsequently play out many of these relationship paradigms in their adult lives, and are unable to self-soothe by drawing on memories, images, or experiences of soothing others. Immature, maladaptive defenses, and ways of regulating emotion, as well as an inability to form complex, integrated representations of others, further contributes to interpersonal instability. Kernberg, a progenitor of psychoanalytic theories pertaining to BPD, described his patients with BPD as having "non-specific ego weakness", that is multiple deficits in the psychological practices fostering adaptive functioning, including poor impulse control, low anxiety tolerance, and disordered thinking (Kernberg, 1975).

More recently, Linehan proposed a biosocial theory of BPD (Linehan, 1993). This framework has some important commonalities with the psychoanalytic perspective; for instance, it recognizes the gravitas of an invalidating environment in childhood. However, Linehan's biosocial theory goes further in that it attempts to explain how an individual's biological traits may interact with an invalidating environment to produce BPD symptomology. While psychodynamic theories of BPD emphasized the importance of

emotion dysregulation, in the biosocial model, this is a core feature of BPD (Koerner, 2007). Emotion dysregulation is viewed as a joint outcome of biological disposition, environmental context, and their interaction during development. The dispositional factors include: 1) emotional vulnerability, defined as high sensitivity to emotional stimuli, 2) very intense response to emotional stimuli, 3) slow return to baseline once emotional arousal has occurred, and 4) maladaptive emotion modulation strategies (Linehan, 1993).

In Linehan's model, emotion dysregulation associated with BPD is the combination of an emotional response system that is over-sensitive and over-reactive, coupled with an inability to modulate the resulting strong emotions and reactions. Evidence suggests that individuals with BPD experience more frequent, more intense, and longer lasting aversive emotional states (Stiglmayr et al., 2005). As a result, individuals with BPD tend not to effectively inhibit inappropriate behavior related to strong emotions, and experience difficulty organizing themselves for coordinated action in the service of external goals. A growing body of literature supports these postulates (e.g., Dixon-Gordon, Gratz, Breetz, & Tull, 2013; Ebner-Priemer et al., 2007; Glenn & Klonsky, 2009; Gratz, Rosenthal, Tull, Lejuez, & Gunderson, 2006).

Linehan (1993) frames difficulty regulating affect as a bipartite problem, possessing components of high baseline negative emotional intensity, and high emotional reactivity to emotionally evocative stimuli. These factors may be both the precursors, and maintaining elements of an escalating pattern of maladaptive behavior that occurs in BPD. For instance, Linehan noted that individuals with BPD commonly experience greater than usual emotional distress in response to a stressor—distress that the individual often struggles to

regulate effectively. In response to this distress, the person with BPD may engage in impulsive or aberrant coping behaviors to relieve or ameliorate their discomfort, such as self-harm or substance use. These behaviors frequently give rise to feelings of shame and guilt (Rizvi et al., 2011), which may feed ever-stronger urges to engage in behaviors to relieve the resulting emotional distress. These behaviors are prone to being negatively reinforced (Haines, Williams, Brain, & Wilson, 1995; Wise & Koob, 2014), and as a result can become conditioned automatic responses to emotional stressors. As such, acute stressors, even when relatively innocuous, can be problematic for individuals with BPD, as they have been shown to lead to a cascade of escalating dysregulation that over time may become ensconced (Selby, Anestis, Bender, & Joiner Jr, 2009; Selby & Joiner Jr, 2009). Emerging evidence suggests that individuals with BPD experience more frequent and longer lasting aversive states (Selby et al., 2009; Stiglmayr et al., 2005), and that problems in ANS functioning may contribute to these difficulties in emotion regulation (Corrigan, Davidson, & Heard, 2000; Ebner-Priemer et al., 2005; Juengling et al., 2003; Leichsenring, Leibing, Kruse, New, & Leweke, 2011).

Borderline Personality Disorder and Co-occurring Substance Use

BPD frequently co-occurs with substance use disorders (SUDs; Dimeff et al., 2000; Eddie, Hunter-Reel, Epstein, & Cohn, 2015; Grant et al., 2008; Regier et al., 1990), and is associated with poorer short- and long-term treatment outcomes for these respective disorders (D. A. Dawson et al., 2005; Hilsenroth, Holdwick Jr, Castlebury, & Blais, 1998; Hunter-Reel, Epstein, McCrady, & Eddie, 2014). Additionally, SUDs are thought to exacerbate BPD symptomology (Axelrod et al., 2011; Links, Heslegrave, Mitton, van

Reekum, & Patrick, 1995). While Kreek and Koob (1998) posit that affective and emotional instability is a common precursor to SUDs in all people, others argue that affective and emotional volatility characteristic of BPD make this population particularly prone to “self-medication” (Trull et al., 2000).

Healthy individuals are generally able to regulate emotional responses to environmental challenges, and recover quickly after emotional arousal (Gratz, Rosenthal, Tull, Lejuez, & Gunderson, 2010; M. Z. Rosenthal et al., 2008). On the other hand, as already noted, those exhibiting symptoms characteristic of BPD often demonstrate hypersensitivity to perturbation by interoceptive or exteroceptive cues (e.g., Ayduk et al., 2008; Lynch et al., 2006). One result is affective instability due to a marked reactivity of mood, resulting in emotional responses in individuals expressing high levels of BPD symptoms that are likely to be inappropriate in content, magnitude, and/or duration that is ultimately indicative of a loss of behavioral flexibility (Donegan et al., 2003; Ebner-Priemer et al., 2007). Diminished behavioral flexibility commonly leads to individuals with BPD resorting to aberrant emotion regulation strategies such as substance use (Gratz & Tull, 2010).

Although acute substance use may to a certain extent reduce negative affect in the moment (Cox & Klinger, 2011), chronic, heavy substance use tends to add negative affect and reduce biobehavioral flexibility, while impairing neural (Koob & Le Moal, 2001) and physiological control of affective states (Eddie et al., 2013; Ingjaldsson, Laberg, & Thayer, 2003; Mehta et al., 2001; Quintana, McGregor, Guastella, Malhi, & Kemp, 2013), leading

to a vicious cycle that contributes to the escalating nature of substance use problems in individuals with BPD.

Emotion as a Biobehavioral Construct

Emotion has been conceptualized as a complex expression of allostatic regulation, that is, the capacity to achieve homeostasis through psychophysiological change (Lehrer & Eddie, 2013; McEwen & Wingfield, 2003; Sterling & Eyer, 1988). Hagemann and colleagues (2003) considered emotion “... an organismic response to an environmental event that facilitates rapid mobilization for action”, noting that, “This response involves multiple systems of the organism, such as cognitive, behavioral, and autonomic sub-systems.” (p. 80) This conceptualization is in line with current theories of emotion (e.g., Izard, 2009; Thayer & Lane, 2000). Emotion and its antecedents are complex biobehavioral phenomena, which play a crucial role in a myriad of cognitive processes.

In terms of in-the-moment behavior, the cognitive components of emotion, and their concomitant physiological processes allow an individual to function effectively in the world by regulating processes such as dynamic hematic perfusion of muscles and organs, and the appropriate release of hormones such as norepinephrine and cortisol (Thayer & Lane, 2000). When these systems are working well, it affords an individual flexible adaptability to changing environmental demands (Damasio, 2001; Thayer & Lane, 2009).

Psychopathological states, on the other hand, may represent a loss of flexibility in such processes. Thayer and Lane (2000) assert that disorders of affect, such as generalized anxiety disorder and major depression, are distorted emotional state-spaces in which individuals are unable to appropriately shift interoceptive resources in response to

moment-to-moment environmental demands. In essence, an individual is unable to express an appropriate response (e.g., chronically blunted affect in depressive disorders), or is unable to inhibit an inappropriate response (e.g., chronic hyper-arousal in anxiety disorders). Further, attendant autonomic rigidity is characterized by impaired capacity to generate or alter physiological responses in synchrony with emotional or environmental challenges (Appelhans & Luecken, 2006). This may result in emotional arousal being maintained longer than is optimal, leading to stress of underlying autonomic processes (McEwen, 2000).

The breakdown of effective emotional responding may result in behaviors that further exacerbate and maintain regulatory dysfunction (Lehrer & Eddie, 2013; Strauman, 2002). For instance, an inability to respond appropriately to social cues may lead an individual to feel social anxiety, resulting in isolation behaviors (Kikusui, Winslow, & Mori, 2006). In turn, isolation behaviors may lead to a weakening of emotion regulation systems because these systems are not being appropriately stimulated and exercised (Thayer & Lane, 2000).

The same theoretical framework can be applied to BPD. For instance, challenges regulating emotion commonly result in emotional outbursts, which may serve to exact significant strain on interpersonal relationships (Lieb et al., 2004). When relationships disintegrate, feelings of loss, loneliness and guilt further destabilize the individual with BPD, leading to greater negative emotional loading and possibly co-occurring physiological dysregulation. As a result, emotion regulation becomes all the more difficult.

The Autonomic Nervous System

Physiological components of emotion regulation may be studied objectively through careful observation of biological functions. Although much previous research on emotion has sought to elucidate the neural pathways in the central nervous system that mediate this capacity, a growing body of work also is seeking to identify emotion regulation processes embedded in the autonomic nervous system (ANS).

The ANS is subdivided into the sympathetic and parasympathetic branches, which innervate all the visceral organs. With regards to emotion regulation, however, its innervation of the cardiovascular, pulmonary, and endocrine systems is of greatest import (Card & Sved, 2011; Hagemann et al., 2003; Iversen, Iversen, & Saper, 2000). These branches work in an antagonistic, yet complementary fashion. The sympathetic branch is responsible for the rapid mobilization of resources to prepare the individual to respond to a stressor or task (Bates & Buckman, 2013). Increases in HR, and BP are characteristic of sympathetic arousal (Kemeny, 2003). The parasympathetic branch, in contrast, performs an inhibitory role, reducing metabolic output and bringing systems back to resting baseline during periods of safety and stability (Saper, 2002).

Porges (2001) has theorized that the human ANS evolved in three stages, each typified by the acquisition of an autonomic structure that plays a specific role in affective and social processes. He speculates that early in human evolution, we acquired slow responding, unmyelinated, parasympathetic nerves that supported simple immobilization behaviors such as freezing in response to a threat, mainly through parasympathetic inhibition of HR via the dorsal vagal complex. He proposed that the capacity for

mobilization responses associated with the sympathetic nervous system evolved later, and that fast acting, myelinated, parasympathetic nerves in the were acquired most recently. This most recent acquisition, which he termed the ventral vagal complex, has afferent fibers terminating in the nuclei of the facial nerves that are also responsible for head turning, listening, vocalization, facial expression, and other socially important behaviors.

Porges' polyvagal theory posits that the ability of the ventral vagal complex to withdraw its inhibitory influence allows humans to rapidly engage and disengage, as necessary, with their exteroceptive milieu, without the metabolic cost of activating the sympathetic nervous system. As such, sympathetic activation is only engaged when parasympathetic withdrawal is insufficient to meet the demands of a task. Porges also noted the importance of dual innervation of the heart by the disparate branches of the ANS, and how the nervous system's regulation of facial expression, vocalization, and socially important behaviors, are closely intertwined through shared nerve fibers, with the ANS pathways that regulate HR and BP (Porges, 2003, 2009). The interconnectedness of these systems make HRV and BPV particularly useful biomarkers of emotion regulation, especially because specific indices associated with these phenomena differentially reflect sympathetic and parasympathetic activity (Vaschillo, Vaschillo, Buckman, Pandina, & Bates, 2011).

The Central Autonomic Network – Structures

The central autonomic network (CAN)—a key component of the ANS—is a collection of neural structures distributed throughout the brain, but most concentrated in the diencephalon, mesencephalon, and brainstem (Standring, 2008). The CAN plays a

pivotal role in the regulation of biobehavioral functions such as the moment-to-moment modulation of HR, BP, and respiration, which underlie goal directed behavior and adaptability. Further, it is responsible for the integration of both interoceptive and exteroceptive information related to affective arousal (Benarroch, 1993; Hagemann et al., 2003; Thayer & Brosschot, 2005).

Figuratively, the CAN can be thought of as a processing hub that integrates cognitive information from higher brain areas such as the prefrontal cortex, with affective information from lower brain regions such as the midbrain and brainstem, as well as afferent information from the viscera. The CAN processes information from these sources and effects changes throughout the brain and body by efferent signaling, and in doing so, actively modulates physiological arousal in accordance with changing situational demands (Hagemann et al., 2003).

Anatomically, the CAN comprises the insular and medial prefrontal cortices, anterior cingulate cortex, the central nucleus of the amygdala, the bed nucleus of the stria terminalis, the hypothalamus, the periaqueductal gray matter in the midbrain, the parabrachial complex in the pons, the nucleus of the tractus solitarius, as well as the medullary intermediate reticular zone, and the ventral tegmental area in the ventrolateral medulla (Benarroch, 1993). Parallel processes between CAN components allow for multiple avenues for a given autonomic response (e.g., increased parasympathetic or decreased sympathetic activity; Hagemann et al., 2003).

Though there is reciprocal interconnection and parallel organization between CAN structures, as well as crossover in their functionality, most CAN areas have primary roles.

For instance, the central nucleus of the amygdala and the bed nucleus of the stria terminalis form the extended amygdala, which effects autonomic expression of emotional states (Herpertz et al., 2002). These areas lie proximal to, and are heavily interconnected with the hypothalamus (mainly the paraventricular nucleus and lateral hypothalamic areas), which initiates coordinated autonomic, neuroendocrine and biobehavioral responses critical for homeostasis and allostasis, particularly through the action of secreted hormones released into the blood.

The anterior cingulate cortex is an important integration place of visceral, attentional and affective information that is critical for adaptive self-regulation (Benarroch, 1993). Moreover, this area is thought to be involved in the conscious experience of emotion, attentional response to stressors, inhibition of excessive emotion, and the process of self-monitoring of emotional states (Hazlett et al., 2005), making it of particular import to the study of BPD. This is also thought to be a key brain area for the facilitation of emotion based decision making (Etkin, Egner, & Kalisch, 2011; Reiman, 1997).

The paraventricular nucleus provides highly specialized innervation of autonomic relay centers through descending nerve fibers (Li & Kirouac, 2012). The paraventricular nucleus' autonomic outputs are fundamental to coordinated visceromotor, neuroendocrine and behavioral hypothalamic effector mechanisms that control vasopressin, oxytocin, and corticotrophin producing neurons in glands in the brain and viscera (Kc & Dick, 2010). In addition, neurons projecting to the dorsal horn are involved in the processing of physical and psychological pain (Eippert, Finsterbusch, Bingel, & Büchel, 2009).

Other CAN areas, however, are more prominently involved in the processing and relay of afferent signals coming into the brain from the viscera. The nucleus of the tractus solitarius forms an important junction of viscerosensory afferent signals travelling up to the brain via the glossopharyngeal and vagus nerves (Damasio, 2003), and also serves a number of key functions in emotion responding because it is the site of reflexes that control HR, BP, and respiration (Benarroch, 1993). Some afferents from the viscera terminate in subnuclei involved in reflexive adjustments of the heart and other organs, while other afferents project to higher CAN areas to initiate integrated autonomic and endocrine biobehavioral responses (Thayer & Lane, 2000). The nucleus of the tractus solitarius initiates multiple medullary reflexes that control cardiovascular, pulmonary, and endocrine functions, while also feeding this information forward to other CAN areas for further processing (Benarroch, 1993; Porges, 2001). Importantly, this locus also processes afferent signals from baroreflex stretch receptors in visceral artery walls, which are responsible for relaying information about arterial blood pressure to the brain, to ensure appropriate perfusion of blood and allow neurons to function optimally (Andersen & Kunze, 1994). The combined roles of the nucleus of the tractus solitarius in blood perfusion, and integrated autonomic and endocrine biobehavioral responses make this brain structure integral to emotion regulation.

The Central Autonomic Network – Role in Cardiovascular Regulation

While the CAN effects biobehavioral adjustments to affective challenges in a number of ways, its principal effects are mediated by the cardiovascular system (Hagemann et al., 2003). Sympathetic preganglionic CAN neurons synapse onto the stellate ganglia,

which projects to the heart via the thoracic visceral nerve. Sympathetic activation of cardiac function unfolds relatively slowly, usually over the time course of seconds, while myelinated, parasympathetic CAN neurons descend directly to the heart via the vagus nerve, and have a very short latency of response, usually in the order of milliseconds (Berntson et al., 1997; Pumpila, Howorka, Groves, Chester, & Nolan, 2002). Autonomic nervous system dysregulation can be mediated by either of these two pathways. Pathology may arise with parasympathetic withdrawal, or sympathetic over activation. One of the goals of the present investigation is to parse out these differential effects as they might pertain to BPD pathology, with the ultimate goal of enhancing and developing targeted treatments for BPD.

Both sympathetic and parasympathetic efferents converge on the heart's central pacemaker nuclei, the sinoatrial, and atrioventricular nodes, serving to either increase or decrease HR. While sympathetic innervation of the heart is tonically active (i.e., relatively constant), parasympathetic tone is constantly modulated to offset sympathetic effects. Thus, the amount of time, or period, between each pair of successive heartbeats is continually changing depending on the balance of sympathetic and parasympathetic input being received by the heart (Thayer & Brosschot, 2005). This constant flux in neural signaling to the heart contributes to HRV, that is, fine-grained changes in HR in response to interoceptive and environmental stimuli. When working well, such responses are rapid, and appropriate in magnitude.

The viscera's feedback to the CAN through mechanisms such as the baroreflex further contributes to HRV in a continuous loop of modulation (Vaschillo et al., 2011).

Autonomically mediated cardiovascular variability is thus a critical marker of neurovisceral integration and an individual's ability to self-regulate (Appelhans & Luecken, 2006).

Relative reduction in vagally mediated HRV is consistent with the cardiac symptoms of panic disorder (H. Cohen et al., 2000; McCraty, Atkinson, Tomasino, & Stuppy, 2001), as well as the psychological symptoms of poor attentional control (Hansen, Johnsen, & Thayer, 2003), ineffective emotion regulation (Fabes & Eisenberg, 1997; Hagemann et al., 2003; Ruiz-Padial, Sollers, Vila, & Thayer, 2003), and behavioral inflexibility (Fuller, 1992; Pauls & Stemmler, 2003; Sgoifo et al., 2003). Impaired HRV has also been observed in affective pathologies such as anxiety disorders (Kemp, Quintana, Felmingham, Matthews, & Jelinek, 2012; Thayer, Friedman, & Borkovec, 1996; Yeragani et al., 1993) and major depression (Agelink, Boz, Ullrich, & Andrich, 2002; Nahshoni et al., 2004; Udupa et al., 2007). These observations formed the impetus for the present investigation as individuals with BPD struggle with emotion regulation and behavioral flexibility, and commonly experience marked anxiety and depressive symptomology.

Effects of Parasympathetic Vagal Withdrawal

While sympathetic over-excitation can lead to cardiac complications (Esler & Kaye, 2000), reduced vagal tone resulting in disinhibition of sympathetic innervation of the heart, presents a higher risk for numerous cardiac problems (Juster, McEwen, & Lupien, 2010; Thayer, Yamamoto, & Brosschot, 2010). In addition, because parasympathetic vagal tone is responsible for the fine-grained changes in HR from moment-to-moment, when this component of innervation is impaired, the ability for the CAN to affect rapid responses to environmental demands is reduced. As a result, an individual may struggle to respond

appropriately to a stressor, and once aroused, may have difficulty returning to baseline in a timely fashion, as is commonly observed in individuals with BPD (Selby & Joiner Jr, 2009, 2013). Ruiz-Padial and colleagues (2003) tested this postulate using a well established affective-startle response paradigm. They found that participants with low basal levels of high frequency HRV (HF HRV)—an index understood to reflect parasympathetic activation—reacted to neutral, harmless stimuli, as well as positive stimuli, as if they were aversive or threatening. Additionally, they showed evidence of hypervigilance and activation of the defensive behavioral system in response to non-threatening stimuli. Conversely, participants with high basal levels of parasympathetically mediated HF HRV showed responses that were appropriate to the experimental stimuli.

Substance Use, Heart Rate Variability & Affective Control

Both acute (Bates & Buckman, 2011; Bennett et al., 2001; Koskinen, Virolainen, & Kupari, 1994) and chronic substance use reduces basal HRV (Eddie et al., 2013; Ingjaldsson, Laberg, et al., 2003; Malpas, Whiteside, & Maling, 1991), possibly through impairment of higher cortical and midbrain processes that affect cardio-dynamics, and through cardiovascular changes that compromise brain-heart communication. In parallel to the depression literature (Chambers & Allen, 2002), HRV has been shown to increase spontaneously with successful SUD treatment (Minami et al., 2002; Weise, Müller, Krell, Kielstein, & Koch, 1986).

The direct pharmacological effects of substance use may impair neural control of affective states, leading to the escalation of BPD symptomology (Links et al., 1995). Thus, difficulty in regulating affective states may both predispose an individual to use substances

to cope emotionally (Bradley, 2003; Kruegelbach et al., 1993), and as a consequence of substance use, affective regulation may become further impaired. As such, an investigation of the relationship between BPD and autonomic functioning ought to consider substance use. Thus, the present investigation tested whether quantity and frequency of past month and past year substance use, as well as SUD diagnosis, affects autonomic activity at baseline, during a stressor, or during recovery from a stressor, and whether these factors differentially affect individuals with BPD and controls.

Autonomic Functioning in Borderline Personality Disorder

To date, six studies have investigated resting HRV and/or SC in individuals with BPD, compared to non-BPD controls. Most of these studies also included a stressor or cue reactivity component. These investigations produced somewhat mixed findings for HRV at rest, as well as during cue exposure paradigms, although a general pattern of autonomic dysregulation is apparent.

Austin et al. (2007) assessed respiratory sinus arrhythmia HRV (a measure of vagally mediated HRV; Task Force, 1996) in 9 treatment seeking women with BPD not taking medication, and 11 healthy controls matched for age and education at resting baseline, and in response to a films depicting interpersonal conflict. Women with comorbid psychopathology were excluded from the study. The authors found participants with BPD showed a trend towards lower baseline HRV than controls. The non-significant effect, however, may have been attributable to their small sample size.

Notably, the authors also observed that HRV in the BPD group decreased during viewing the films depicting interpersonal conflict, while HRV increased in the control

group. Austin and colleagues (2007) interpreted this observation through Porges' polyvagal perspective. They inferred that the BPD group was exhibiting a physiological state of preparedness for defensive behaviors, while viewing the conflict films, as evinced by lower HRV resulting from vagal withdrawal. Controls, on the other hand, were exhibiting a physiological state that would support social engagement behaviors, such that they demonstrated increased HRV in response to viewing conflict. The authors posited that increased vagal influence of the heart would support spontaneous social engagement behaviors. The singular HRV measure utilized in that study, however, makes the clear interpretation of results problematic. It is not clear, for instance, how activity in the sympathetic nervous system may have influenced their findings.

Ebner-Priemer et al. (2007) conducted a quasi-experimental, ambulatory study in which they monitored HRV in 50 treatment-seeking women and men with BPD (mean age = 31.3; $SD = 8.1$) and 50 healthy controls (mean age = 27.7; $SD = 6.8$) over a 24-hour period using mobile HRV recording devices, and ecological momentary assessment. Medication was not exclusionary. As predicted, the authors observed that participants with BPD experienced significantly more negative affect than controls during the 24-hour ambulatory period, in terms of frequency of negative emotions, as well as their intensity (see Ebner-Priemer et al., 2008 for detailed discussion of these effects).

In terms of cardiac indices, there were significant differences within the BPD sample, such that participants on medication evinced lower HR and lower high frequency HRV (HF HRV; a measure understood to reflect vagally-mediated, parasympathetic influence on the heart) over the 24-hour recording period (after controlling for movement

and exercise) than BPD participants not on medication. These effects were maintained during the night when participants were asleep, suggesting these differences are directly pharmacologically mediated, rather than being secondary effects of the medication on mood and/or cognition. In addition, there was no significant difference between medicated and non-medicated BPD participants on self-reported emotions. As a result of the differences between these BPD sub-groups, the investigators' limited their investigation to BPD participants not on medication and controls, in doing so reducing their power to detect significant differences between BPD and control participants. They found BPD participants not on medication had higher ambulatory HR than controls, though these groups were not significantly different in terms of HRV.

Kuo and Linehan (2009) assessed differences in resting HRV, as well as skin conductance response—a measure of sympathetic activity—in 20 treatment seeking women with BPD (mean age = 23.6), 20 age matched women with social anxiety disorder as an affective control group (mean age = 23.1), and 20 age matched healthy females as a control group (mean age = 23.3). Groups were compared on these measures at resting baseline, as well as in response to emotionally arousing cues. Medications other than SSRIs were exclusionary.

Each study volunteer participated in two sessions. In one session, after baseline physiological and psychological assessment, participants were exposed to a series of emotionally evocative stimuli—films shown to evoke either sadness, anger, or fear. A neutral film was also included as a control in their counter-balanced design. In another session, participants were exposed to their self-written, personally relevant imagery scripts

after being instructed to write about a vivid or recent event in which they felt sad, afraid, angry, or as a control, emotionally neutral. When in the experimental session, these scripts were read back to them, and they were asked to imagine themselves back in the described situation.

As predicted, questionnaire measures capturing baseline emotion regulation difficulties indicated participants with BPD experienced significantly more emotion dysregulation than participants in either control group, as measured by the Difficulties in Emotion Regulation Scale (Gratz & Roemer, 2004), the State-trait Anger Inventory (Spielberger, Jacobs, Russell, & Crane, 1983). In addition, the BPD group had lower HF HRV at baseline compared to the control groups. BPD participants also demonstrated higher resting skin conductance response levels than controls, indicating greater baseline sympathetic activation. However, BPD participants and social anxiety disorder controls were not significantly different in terms of basal levels of skin conductance response, suggesting that individuals with social anxiety disorder experience similar resting levels of sympathetic arousal to individuals with BPD.

Notably though, in contrast to Austin et al.'s (2007) findings and the authors' predictions, there were very few significant between group differences in terms of physiological change from baseline to the emotionally evocative cues. One significant difference was, while viewing the sad film, BPD participants showed an increase in HRV and decrease in skin conductance response, while social anxiety disorder controls evinced the opposite effect. Compared to healthy controls, BPD participants showed the same pattern of divergent skin conductance response responding, but no difference in HRV

responding. The authors speculated that this may be attributable to BPD participants engaging in cognitive emotion regulation strategies during the sad film. Overall though, participants with BPD did not demonstrate substantively greater physiological responses to emotional stimuli.

Taken together, these findings offer partial support for Linehan's biosocial theory of BPD. In keeping with current theories of psychophysiological emotion regulation, lower baseline HRV in participants with BPD is indicative of vulnerability to emotion dysregulation. Participants with BPD also indicated greater self-reported baseline negative emotionality, which the authors suggest is a corollary of higher baseline skin conductance response levels in this group. Though this link is plausible, they did not provide empirical evidence to support this claim, as they did not report a correlation between these two measures. Regardless, these findings suggest that individuals with BPD are not generally more physiologically reactive to emotionally evocative stimuli than controls. Moreover, the extreme intensity of negative emotionality associated with BPD may be better accounted for by higher baseline levels of negative affect, and impaired at-rest autonomic regulation.

Around the same time, Weinberg et al. (2009) assessed respiratory sinus arrhythmia HRV at resting baseline, and during an arithmetic stress paradigm intended to frustrate participants and elicit an emotional response. Their sample was 72.5% female, and included 12 individuals from an introductory psychology course who were deemed likely to have BPD based on their scores on the McLean Screening Instrument for BPD (Zanarini et al., 2003), and 28 individuals who scored very low on the instrument (mean age = 19.9; $SD = 5.0$). The authors used a McLean Screening Instrument cutoff score of 5 out of 10 to

determine likely BPD. This may have been an intuitive decision based on the fact the DSM-IV-TR requires 5 BPD symptoms be present to diagnose this disorder. The McLean Screening Instrument's authors, however, recommend a minimum cutoff score of 7 out of 10, based on their study of the measure's diagnostic efficiency (Zanarini et al., 2003). It is possible then that Weinberg et al.'s BPD sample included individuals who were likely sub-threshold for BPD.

As predicted, the authors found that the participants scoring high on the BPD screening questionnaire self-reported greater frustration during the arithmetic task. They also exhibited lower parasympathetically mediated HRV at baseline, during the stressor task, and during a recovery period compared to controls with fewer BPD symptoms. In addition, participants high on BPD symptomology displayed a differing pattern of autonomic activation through the course of the study. Although they demonstrated significantly higher sympathetic activation compared to controls during each task, including during baseline assessment, they also evinced a pattern of increasing sympathetic arousal (reflected by the cardiac sympathetic index; Toichi, Sugiura, Murai, & Sengoku, 1997) from the first to second half of the stressor task. Controls, on the other hand, demonstrated a pattern of reducing sympathetic arousal. The authors inferred that participants with BPD were becoming increasingly aroused during the stressor, and were more inclined than controls to revert to a phylogenically older fight-or-flight response. Controls, on the other hand, appeared to be habituating to the task. Contrary to their expectations, the authors found no differences in parasympathetically mediated HRV through the course of the stressor task, suggesting sympathetic activation, and not vagal

withdrawal was driving increasing arousal in the BPD group. It may be that stress tasks elicit different autonomic responses than affectively evocative cues that elicit emotions such as sadness, fear, and anger.

More recently, Dixon-Gordon and colleagues (2011) assessed HRV and skin conductance response in an study primarily investigating the role of negative emotions and social problem solving in BPD. Their sample consisted of 87 female university students under 60 years of age with high ($n = 26$), medium ($n = 32$), or low ($n = 29$) levels of BPD features according their scores on the Personality Assessment Inventory – Borderline Features Scale (PAI-BOR; Morey, 1991). High scorers returned PAI-BOR scores typically found in individuals with a formal BPD diagnosis, low scorers had scores at or below the average for college students, as reported by Morey (1991), and medium scorers returned scores between these two groups. The total sample's mean age was 21.6 ($SD = 5.6$).

Participants HRV and skin conductance response were recorded across seven, five-minute tasks. These included, 1) a true baseline, 2) a vanilla baseline (Jennings, Kamarck, Stewart, Eddy, & Johnson, 1992), 3) presentation of three randomly selected means-ends problem-solving test procedure scenarios (MEPS; Platt, Spivack, & Bloom, 1975), a test designed to assess individuals' ability to successfully resolve interpersonal problems, 4) a second vanilla baseline task, 5) a negative emotion induction procedure in which participants listened to a recording of interpersonal conflict, and were asked to imagine themselves in that scenario, 6) three more randomly selected MEPS scenarios, and 7) a final true baseline. Participant medications and substance use were not controlled for. Due

to technical errors and artifact, HRV data from 13 participants, and SC data from 20 participants was lost.

The authors did not observe any significant group, or group \times time effects for respiratory sinus arrhythmia HRV. Though their non-significant omnibus test precluded post hoc tests for baseline between group differences in HRV, their results suggested a linear relationship between BPD symptomology and HRV, such that the group high in BPD features had the lowest HRV at baseline, while the group low in BPD features had the highest HRV, and the medium group had HRV levels in between the high and low groups.

Main effects of group and time for skin conductance response were observed, although post hoc test results for these main effects were not reported. Though the group \times time interaction omnibus test for skin conductance response was not significant, the authors reported that the group high in BPD features showed significantly more skin conductance response during the emotion induction compared to baseline, while the group low in BPD features showed no significant changes in skin conductance response from baseline to emotion induction.

Interpreting Dixon-Gordon et al.'s results is made challenging by the omission of certain post hoc test results from the paper. In addition, their complex paradigm utilizing multiple stressors may have not been ideal for the psychophysiological component of their study, and could have potentially confounded results. Though their figures suggested a linear relationship between BPD symptomology and baseline levels of HRV, the results reported do not formally afford this interpretation. In addition, while they reported

significant post hoc test results for skin conductance response, the non-significant omnibus test for the group \times time interaction means these post hoc results may not be valid.

Most recently, Gratz and colleagues (2013) assessed emotion regulation capacity and HF HRV in women 18-60 years of age with BPD ($n = 26$; mean age = 24.9, $SD = 11.3$), BPD and co-occurring avoidant personality disorder (AVPD; $n = 13$; mean age = 24.6, $SD = 8.8$), and as controls with psychiatric difficulties but not BPD, women reporting mood, relationship, and/or impulse control difficulties ($n = 18$; mean age = 24.1, $SD = 11.5$). Participants were assessed at resting baseline, and during a modified version of the Paced Auditory Serial Addition Task (PASAT-C; Lejuez, Kahler, & Brown, 2003), a stress paradigm that tests individuals willingness to experience distress in order to pursue goal-directed behavior. Participants using psychotropic medications other than anti-depressants were excluded, as were participants experiencing manic, hypomanic, or depressive mood episodes in the past two weeks, as well as active substance use problems, and primary psychosis.

As predicted, both BPD groups showed a general pattern of lower, self-reported emotion regulation capacity in comparison to the non-BPD controls, as measured by the Difficulties in Emotion Regulation (DERS; Gratz & Roemer, 2004) subscales. Although results did not reveal general, significant differences in emotion regulation difficulties between BPD participants with and without AVPD, BPD participants with (versus without) AVPD reported greater difficulties accessing effective emotion regulation strategies.

With regards to the psychophysiological outcomes, at resting baseline, the authors did not find significant differences in HF HRV between participants with BPD (with and

without co-occurring AVPD), and non-BPD controls. Notably however, in response to the PASAT-C stressor task, participants with BPD (and not AVPD) and non-BPD controls demonstrated an increase in HF HRV, whereas BPD participants with AVPD exhibited a decrease in HF HRV. In line with Porges' poly-vagal theory, the authors interpreted increased HRV in the BPD without AVPD and non-BPD control groups as an adaptive emotional response, while the reduced HRV response in the BPD with AVPD group to be indicative of poor emotion regulation capacity.

The heterogeneity of the samples utilized in these investigations may explain some of the divergent findings between studies. Austin et al. (2007) used an all female treatment-seeking sample but excluded individuals with co-occurring psychopathology, or who were taking medication. Ebner-Priemer (2007, 2008) tested a mixed sex sample, excluding more severe comorbid psychopathology, and controlling for medication in their analysis. Kuo and Linehan (2009) tested an all female, treatment-seeking sample, and allowed for comorbid psychopathology, as well as some medications. Weinberg et al. (2009) assessed a non-treatment seeking sample of female and male college students suspected of having BPD, without formally diagnosing BPD with a clinical interview, or screening for comorbid psychopathology and medication. Dixon-Gordon et al., (2011) also assessed a non-treatment seeking sample of female and male college students suspected of having BPD, and allowed for comorbid psychopathology, and medications. Finally, Gratz et al., (2013) assessed an all female sample, excluding participants using psychotropic medications other than anti-depressants, and with certain co-occurring, active psychological disorders.

The relative merit of these respective facts has been argued in the literature. Borderline personality disorder is highly comorbid with a number of other psychological disorders (Glenn & Klonsky, 2009), so it has been suggested that allowing for comorbidity in study samples gives researchers a better representation of the population. The present investigation excluded volunteers with active psychosis, although comorbid disorders associated with anxiety, depression or substance use were not exclusionary, as these represent important potential moderators of the relationship between groups in the present study.

The question of whether to examine a single sex, or a mixed male and female sample also bore consideration. At least one group measuring mean SC in individuals with BPD has found significant differences between sexes in sympathetic responding to negatively valenced picture cues. Herpertz's group found women, but not men with BPD demonstrated hypoarousal to negatively valenced cues, though it should be noted that the men were from a psychiatric prison population, while the women were treatment seekers in the community (Herpertz et al., 2002; Herpertz, Kunert, Schwenger, & Sass, 1999; Herpertz et al., 2001). Although the majority of individuals with BPD are female, and an all female sample may seem desirable, such samples are not truly representative of the BPD population. As such, this investigation tested women and men with BPD in approximate proportion to their representation in the general population. Additionally, controls were sex matched to experimental group participants.

The issue of medication effects on psychophysiological measures must also be addressed. Previous studies have shown approximately 75% of individuals with BPD utilize

psychotherapeutic mediations (Zanarini, Frankenburg, Hennen, & Silk, 2004). Excluding persons with BPD on medication may inadvertently exclude individuals with more severe BPD, who are more likely to be on medication (Sansone, Rytwinski, & Gaither, 2003). Ebner-Priemer et al.'s (2007) finding that BPD participants on medication were significantly different in terms of HRV to those not on medication indicates the importance of considering this factor. The present study thus retained volunteers on psychiatric medications, although participants were strategically scheduled to reduce medication effects, and medications known to affect the cardiovascular system, such as hypertension medications, were exclusionary.

Another point bearing consideration is that the studies reviewed here assessed for BPD in different ways, that is, some utilized clinical interview while others relied on self-report questionnaires. In addition, the majority of the reviewed studies did not directly report BPD severity in their samples. Because BPD is a heterogeneous disorder that varies in severity from person to person (Lieb et al., 2004), the present investigation considered BPD severity in its analyses.

Notably, with the exception of an early study by Herpertz et al. (1999) that measured HR and SC, none of the studies using treatment-seeking BPD participants attempted to control for participant time in treatment. This is an important consideration. A participant nearing the end of a one-year course of Dialectical Behavioral Therapy may be far less affectively dysregulated than someone just beginning treatment, or may self-report quite differently. For instance, Ebner-Priemer et al. (2007) found that BPD participants in ongoing Dialectical Behavioral Therapy were better at identifying emotions

than participants about to start treatment. The present study, therefore, explored potential effects of time in treatment.

Age is another factor that must be taken into consideration when studying autonomic measures, given age is negatively correlated with autonomic functions such as HRV (Agelink et al., 2001; Lehrer et al., 2006). Although the majority of psychophysiology studies reviewed here had fairly youthful samples with relatively low variance in age, age remains an important consideration. As such, the present study age matched controls to the BPD group.

Given large inter-individual differences in physiology, and the commonness of cardiac abnormalities, statistical outliers are also an important consideration when studying autonomic process like HRV. Failure to appropriately deal with outliers can produce spurious results. It is possible that sub-group differences may have been due to a small number of very low, or very high scores. The present study included careful visual and statistical inspection of all data to appropriately consider potential outlier effects.

It also should be noted that the emotion evoking stimuli varied across studies. The problem of reliably evoking an affective response across different individuals is well known (Herpertz et al., 2002; Sloan et al., 2010). It is therefore possible that differences in findings between the aforementioned studies may be related to differences in the stimuli used. It is currently unknown whether some types of stressors differentiate BPD better than others. A stimulus that taps into multiple BPD sensitivities may be most useful in cue reactivity paradigms in individuals with BPD (Herpertz et al., 2002). The present

investigation thus utilized a stimulus set that was designed to engage multiple BPD sensitivities (Sloan et al., 2010).

Ebner-Priemer and colleagues' (2005; 2009) finding that individuals with BPD reporting high state dissociation showed lower electromyographic acoustic startle response than those reporting low dissociation highlights an important consideration for the present investigation. Ebner-Priemer's observation could explain some of the divergent findings in stressor response in the BPD psychophysiology literature, and may be a corollary of Porges' proposed vagal freeze-response (Porges, 2003). It is possible that there are distinct sub-groups of response types amongst individuals with BPD. As such, the present investigation assessed dissociative symptomology as a potential moderator of cue reactivity.

Finally, because respiration influences HRV (Vaschillo et al., 2011), the present investigation also considered respiration in its analyses.

Study Rationale

Flexible ANS functioning is an important component of emotion regulation, yet the role of autonomic activity in BPD, a disorder characterized by emotion dysregulation, is not well understood. While the findings in the aforementioned literature offer preliminary evidence indicating that individuals with BPD are different than controls on a number of important autonomic measures, it remains to be seen whether attenuated vagal tone, vagal hyporeactivity or potentiated sympathetic activation, or a combination thereof are the primary autonomic underpinnings of the chronic, emotion dysregulation associated with BPD. As such, examination of indicants of autonomic regulation such as indices of heart rate variability (HRV), blood pressure (BP), blood pressure variability (BPV), and skin

conductance variance (SCV) has the potential to contribute significantly to our understanding of affective dysregulation in BPD.

The present investigation extends previous work by examining autonomic functioning in individuals with BPD, using a comprehensive spectrum of HRV indices, as well as BPV, in addition to previously reported measures such as HR and SC. Moreover, it is the first such study to investigate the effects of chronic substance use on autonomic cue reactivity in individuals with BPD, while controlling for time in treatment, using a mixed male and female sample representative of the BPD population.

This was achieved by comparing individuals with BPD, with differing substance use histories, to healthy controls at three time points, 1) at resting baseline while engaged in a low cognitive demand task, 2) during exposure to emotionally evocative pictures, and 3) during a naturalistic post-perturbation recovery period.

Hypotheses

Preliminary Between-group Psychosocial Comparisons

Participants with BPD, compared to healthy controls, were predicted to have greater basal levels of anxiety and depression, more negative and less positive affect, greater emotion dysregulation, and dissociative symptomology. Participants with BPD were also hypothesized to report greater past month and past year substance use, and have higher rates of lifetime substance dependence.

Associations Between Anxiety and Depression, and Baseline Physiological Measures

Numerous studies have found trait anxiety and depression to be negatively correlated with indices of HRV characterizing parasympathetic activation (e.g., Chang et

al., 2012; Eddie, 2012; Miu, Heilman, & Miclea, 2009). Therefore, within the BPD group, trait anxiety and depression severity were expected to be negatively associated with HRV measures believed to reflect parasympathetic tone, such as the percent of adjacent normal-to-normal intervals greater than 50 milliseconds (pNN50), the root of the mean squared differences of successive normal-to-normal intervals (RMSSD), and high frequency HRV (HF HRV).

Baseline Physiological Between-Group Differences

The majority of work to date suggests individuals with BPD have lower resting parasympathetically mediated HRV, and/or higher HR than controls (Austin et al., 2007; Ebner-Priemer et al., 2007; Koenig, Kemp, Feeling, Thayer, & Kaess, In press; Kuo & Linehan, 2009; Weinberg et al., 2009). As such, it was hypothesized that participants with BPD would have lower resting HRV expressed by standard deviation of all normal-to-normal intervals (SDNN), pNN50, RMSSD, HF HRV, and higher HR during baseline assessment. Although previous psychophysiological investigations of BPD have not included BP indices, because dynamic BP (i.e., BPV) is regulated by the baroreflex mechanism, which is also a key determinant of HRV, it was predicted that participants with BPD would exhibit lower basal, resting systolic blood pressure (SAP) variability, expressed as the standard deviation of SAP (SAPD). In addition, previous work has suggested individuals with BPD have higher resting sympathetic activation than controls (Kuo & Linehan, 2009; Weinberg et al., 2009). As such, participants with BPD were expected to express greater sympathetic activation at rest, compared to controls, as shown by SCV measures.

Between-group Differences During Cue Exposure

To date, Kuo and Linehan (2009) have provided the most thorough investigation of autonomic functioning during emotionally evocative cue exposure in individuals with BPD. In line with Kuo and Linehan's (2009) finding that individuals with BPD reported greater subjective arousal to emotionally evocative stimuli than controls, participants with BPD were predicted to rate the stimuli as more subjectively arousing than their control counterparts. Yet, based on their finding that participants with BPD were not different than controls in terms of change in autonomic activity from baseline to cue exposure, between group differences were not anticipated here.

In contrast, previous findings have shown neurocardiac responses to visual stimuli including positive, negative and neutral pictures, as well as footage of interpersonal conflict, across a range of non-BPD samples, tend to be characterized by decreased parasympathetically mediated HRV (Austin et al., 2007; Bates et al., 2011; Vaschillo et al., 2008). As such, participants in both groups were predicted to respond to the emotionally evocative picture cues with decreased SDNN, HF HRV, and SAPD.

Between-group Differences During the Post-cue Exposure Recovery Period

A growing literature suggests that once perturbed, individuals with BPD experience more pronounced and sustained negative affective states (e.g., Glenn & Klonsky, 2009; Selby et al., 2009; Stiglmayr et al., 2005) than individuals without psychopathology, and that chronic substance use may exacerbate this effect (Axelrod et al., 2011; Links et al., 1995). Based on these findings, it was postulated that this pronounced and sustained negative affective state co-occurs with sustained autonomic activation. As such, participants

with BPD were predicted to demonstrate sustained increases in HR and SCV, and decreases in SDNN, HF HRV, and SAPD during the post-stimulus exposure period, while control group participants were predicted to return to basal levels of HR, SDNN, HF HRV, SAPD, and SCV during this task.

Effects of Substance Use in Participants with Borderline Personality Disorder

Because chronic, heavy substance use is negatively associated with HRV (Eddie et al., 2013; Ingjaldsson, Thayer, & Laberg, 2003; Quintana et al., 2013), substance use measures such as frequency of past month and past year substance use, as well as quantity of alcohol consumed in a typical week in the past month, were expected to be negatively associated with basal measures of HRV in the BPD sample.

Substance use may lead to the impairment of neural control of affective states, and thus exacerbate BPD symptomology (Axelrod et al., 2011; Kruegelbach et al., 1993; Links et al., 1995). If this is the case, individuals reporting greater substance use may experience larger autonomic responses to stressors, and slower return to autonomic baseline following perturbation. Thus, within the BPD group, substance use was hypothesized to positively predict cue exposure response, such that greater past month and past year substance use would predict greater autonomic responses to emotionally evocative pictures. Further, it was hypothesized that substance use would be negatively associated with cue exposure recovery, such that greater substance use measured by quantity and frequency of past month and past year use would predict less autonomic recovery from exposure to emotionally evocative pictures.

Materials & Methods

Participants

Fourteen of 22 study participants with BPD were recruited from the Dialectical Behavior Therapy Clinic at Rutgers University (DBT-RU), an outpatient program at the Graduate School for Applied and Professional Psychology (GSAPP) that provides comprehensive Dialectical Behavior Therapy services to individuals in the community, as well as Rutgers University students. DBT-RU provides care to adults who meet criteria for BPD and have a history of self-injurious or suicidal behavior. DBT-RU diagnoses psychopathology using the Diagnostic Statistical Manual of Mental Disorders IV, text-revision (DSM-IV-TR), and assesses incoming patients for psychopathology using the Structured Clinical Interview for DSM-IV-TR, Sections I & II (SCID-I & SCID-II; First, Gibbon, Spitzer, Williams, & Benjamin, 1997; First, Spitzer, Gibbon, & Williams, 2002). These diagnostic data were utilized in the present investigation.

Eight of 22 study participants with BPD were recruited from other Dialectical Behavior Therapy clinics in central New Jersey. These participants were formally assessed for BPD using the BPD section of the SCID-II, and were also administered the SCID-II screener (First, 1997). To minimize participant burden based on the amount of compensation provided, these participants were asked to self-report current and previous psychiatric diagnoses aside from BPD, rather than undergo the full SCID-I and SCID-II interviews.

Control group participants ($N = 22$) were recruited from the Rutgers, and broader central New Jersey community via flyers, and were matched on sex and mean age to BPD

participants. Potential control group participants were screened for psychopathology using the SCID-I and SCID-II screeners in combination with a brief, structured clinical interview. Participants demonstrating any indication of psychopathology were thanked for their time and not invited to participate in the study.

Study inclusion criteria for BPD participants were a DSM-IV-TR (2000) diagnosis of BPD confirmed by clinical interview using the SCID-II. Co-occurring personality disorders were allowed for BPD participants. Any DSM-IV-TR disorder diagnosis was, however, exclusionary for control participants. Serious medical or neurological conditions and active psychosis and medications directly affecting the cardiovascular system (such as hypertension medicines) were exclusionary for both groups. For participants with BPD, psychiatric medications were allowed.

All study participants were required to be over 18 years of age.

Background Information Measures

An in-laboratory questionnaire was administered to assess participant demographics including race, ethnicity, income, and marital status. This questionnaire also assessed time in Dialectical Behavior Therapy treatment, and total lifetime psychological treatment received, as well as current medications.

Psychological Measures

A battery of questionnaires was utilized to assess current BPD symptomology, substance use, as well as anxiety, and depression. Because state dissociation has been found to affect startle response (Ebner-Priemer et al., 2005; Ebner-Priemer et al., 2009), a questionnaire on trait dissociative tendencies was also administered. Furthermore, because

health behaviors such as exercise may affect physiological indices, exercise behaviors were also assessed.

Acceptance and Action Questionnaire II (AAQ-II)

The AAQ-II (Bond et al., 2011) is a 10-item self-report measure of acceptance, experiential avoidance and psychological inflexibility. Higher scores suggest greater psychological flexibility. The AAQ-II has satisfactory structure, reliability, and validity, with an alpha coefficients ranging from .78 - .88, and the 3- and 12-month test-retest reliability of .81 and .79 respectively, and adequate discriminant validity (Bond et al., 2011).

Beck Depression Inventory (BDI)

The BDI (Beck, Steer, & Brown, 1986) is a 21-item self-report instrument used to assess depression. The BDI uses a 4-point Likert-type scale. Higher scores indicate greater depression. The BDI has high internal consistency ($\alpha = .81$) with test-retest reliability of .96 (Beck, Steer, & Carbin, 1988; Sprinkle et al., 2002), and high content validity (Richter, Werner, Heerlein, Kraus, & Sauer, 2000).

Borderline Symptom List 23 (BSL-23)

The BSL-23 (Wolf et al., 2009) is a 23-item self-report questionnaire that assesses BPD symptom expression. Participants rate the degree to which they experienced listed symptoms using a scale from 0 (Not at all) – 4 (Very strong). An additional 11 items ask participants to report BPD associated behaviors using a scale of 0 (Not at all) – 4 (Daily or more often). The BSL-23 has high internal consistency ($\alpha = .95$), and has established discriminant validity (Bohus et al., 2008).

Difficulties in Emotion Regulation Scale (DERS)

The DERS (Gratz & Roemer, 2004) is a 36-item self-report instrument designed to measure multiple aspects of emotion regulation. Higher scores suggest greater challenges with emotion regulation. The DERS provides six subscales, including non-acceptance of emotional responses, difficulties engaging in goal directed behaviors, impulse control difficulties, lack of emotional awareness, limited access to emotion regulation strategies, and lack of emotional clarity. It has high internal consistency, with alphas ranging from .80 to .89. In addition, the DERS has good test-retest reliability, and adequate construct and predictive validity (Gratz & Roemer, 2004).

Dissociative Experiences Scale-II (DES-II)

The DES-II (Carlson & Putnam, 1993) is a 28-item self-report measure of the frequency of dissociative experiences. Higher scores indicate greater dissociative tendencies. The scale has very good internal consistency with an alpha of .92 (Zingrone & Alvarado, 2001), and has shown acceptable construct validity (Frischholz et al., 1992).

Exercise and Sleep Questionnaire

An in-lab exercise and sleep questionnaire developed by the Cardiac Neuroscience Laboratory was used to assess participant sleep hygiene and exercise patterns (Udo et al., 2013).

Positive and Negative Affect Schedule (PANAS)

The PANAS (Watson, Clark, & Tellegen, 1988) is a 20 item self-report instrument that measures current positive and negative affect using a 5-point Likert-type scale. The PANAS can be used to assess present moment affect, or past week affect, depending on the

instructions given. For the present investigation, participants were given the following instructions, “Indicate to what extent you feel this way right now, that is, at the present moment”. The PANAS has high internal consistency with alphas ranging from .86 to .90, with test-retest reliability ranging from .68 to .71 (Watson et al., 1988).

State-Trait Anxiety Inventory, Form Y (STAI-Y)

The STAI-Y (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983b) assesses both state and trait anxiety using 40 questions. All items are rated on a 4-point scale (e.g., from “Almost Never” to “Almost Always”). Higher scores indicate greater anxiety. Internal consistency coefficients for the scale have ranged from .86 to .95; test-retest reliability coefficients have ranged from .65 to .75 over a 2-month interval (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983a). Test-retest coefficients range from .69 to .89. Considerable evidence attests to the construct and concurrent validity of the scale (Barnes, Harp, & Jung, 2002).

Structured Clinical Interview for DSM-IV-TR – Section I (SCID-I)

The SCID-I (First et al., 2002) assesses lifetime and current DSM-IV-TR Axis I psychopathology. Good inter-rater reliabilities have been reported for the SCID-I, with kappas from .84 to 1.00 (Schneider et al., 2004). Overall inter-rater reliability for the alcohol modules of the SCID-I has been reported in the range of kappa = .65 to .75 (Lobbestael, Leurgans, & Arntz, 2011; Williams et al., 1992).

Structured Clinical Interview for DSM-IV-TR – Section II (SCID-II) Screener

The SCID-II screener (First, 1997) measures the presence of lifetime and current personality disorder symptomology, using a series of brief questions requiring a yes or no

response. It is used as a screening tool to determine the necessity of administering the full SCID-II diagnostic interview battery (First et al., 1997) for specific personality disorders. The SCID-II screener is well validated (Jacobsberg, Perry, & Frances, 1995). It has high inter-rater reliabilities with kappas of .77 to .93 (Jane, Pagan, Turkheimer, Fiedler, & Oltmanns, 2006; Schneider et al., 2004) and good test-retest reliability (Zanarini & Frankenburg, 2001; Zanarini et al., 2000).

Structured Clinical Interview for DSM-IV-TR – Section II (SCID-II)

The SCID-II (First et al., 1997) assesses lifetime and current Axis II personality disorder psychopathology. Good inter-rater reliabilities have been reported for the SCID-II personality disorder diagnoses, with kappas of .89 to .98 (Maffei et al., 1997; Schneider et al., 2004). The SCID-II was only administered if individuals' scores on the SCID-II screener suggested personality disorder pathology.

Substance Use Measures

Participants with BPD recruited from DBT-RU had been previously screened for substance use disorder status using SCID-I interview (First et al., 2002), while participants with BPD recruited from Dialectical Behavior Therapy clinics other than DBT-RU were asked to self-report any history of substance use disorders during screening. Control participants were screened for substance use disorders using the SCID-I screener (First, 1997) and excluded if a substance use disorder was deemed possible.

Immediately before the experimental session, self-report questionnaires were administered to assess all participants' past month and past year substance use (Buckman, White, & Bates, 2010; Udo et al., 2009). An alcohol use questionnaire asked such

questions as, “How often did you drink any alcoholic beverage within the past month?” and “Over the past year, how many drinks did you usually (more than half of the time) have per occasion?” The drug use questionnaire asked such questions as, “Have you used [the following drugs] in the past thirty days?” and “How many/much did you use per day?”

Although self-reporting about potentially sensitive issues such as substance use seems intuitively problematic (Tourangeau & Yan, 2007), self-report methods have consistently been shown to be a reliable and valid approach for measuring alcohol and drug consumption in both treatment seeking, and non-treatment seeking samples (Calhoun et al., 2000; Del Boca & Darkes, 2003; Winters, Stinchfield, Henly, & Schwartz, 1990).

Emotional Picture Stimuli

Sloan and colleagues (2010) generated a stimulus set pertinent to core themes frequently noted in clinical observations (e.g., Lieb et al., 2004; Rizvi & Salters-Pedneault, 2013) and self-report studies (e.g., Herpertz et al., 1997; Yen, Zlotnick, & Costello, 2002) of individuals with BPD. The set was developed by having 19 clinicians and clinical researchers who were expert in BPD rate IAPS pictures on how self-referential they imagined they would be to an individual with BPD. Images were judged in terms of how much they depicted or readily implied a situation that a person with BPD would identify as relevant to their experience. Pictures were ranked by level of self-reference. Sloan and colleagues' (2010) top 36 ranked pictures were selected for use in the present study. However, because eight of these images are similar in that they depict interpersonal violence, three of which contain the same actors in different poses, four of these images

(image numbers 6530, 6540, 6550 & 6560) were replaced by other highly ranked, self-referential pictures from the same picture set (images, 2053, 2271, 2800 & 9405). The final BPD specific IAPS picture set is noted in Appendix A.

Physiological Assessment

Electrocardiogram, SC and respiration data were continuously recorded at a rate of 2000-Hz by a Powerlab Acquisition system (ADInstruments, Colorado Springs, CO), while beat-to-beat BP was continuously recorded using a Finometer MIDI (Finapres, Amsterdam). Respiration sensors were calibrated pre-session by having subjects inflate and deflate an 800 ml breathing bag 5 times. Sequences of heart beat-to-beat intervals (RR) were recorded and exported to a WinCPRS software program (Absolute Aliens Oy, Turku, Finland) for analyses and calculation of HRV indices, as well as mean HR. After cubic interpolation of the non-equidistant waveform, the RR sequence was checked for artifacts and irregular beats. Because respiration influences HR and HRV (Berntson et al., 1997), mean respiration frequency was calculated from the thoracic respiration record. All physiological measures were calculated separately for the each task, and then analyzed using time and frequency domain methods. For frequency domain HRV indices, RR spectra were calculated through Fourier analysis (Cooke et al., 1999; Taylor, Carr, Myers, & Eckberg, 1998). Heart rate—expressed as beats per minute—was derived by calculating the average number of R-spikes in the ECG signal occurring each minute during each 6-minute recording period.

Controlling for Substance and Medication Use

Participants were instructed to abstain from alcohol, and other drugs during the 24 hours prior to the laboratory session, as well as to refrain from taking caffeine, or over-the-counter medications on the day of the session. Participants were also instructed not to use products containing nicotine for at least two hours before coming into their session. When individuals were prescribed medications *pro re nata* (as needed) that might affect psychophysiological measures, it was agreed we would reschedule experimental sessions if they needed to take these medications the day of their participation. To ensure participant safety, BPD group volunteers were instructed not to deviate from regular medication regimes. In instances when a participant took a regular daily dose of a prescribed medication that could possibly affect physiology (e.g., a benzodiazepine), sessions were scheduled to allow at least four hours of washout time to minimize acute drug effects.

Procedure

Before phone screening, all interested inquirers were asked to provide oral informed consent. Once oral consent was obtained, the phone screen interview collected basic contact and demographic information, and inquired about exclusionary criteria such as pre-existing medical or neurological conditions. In addition to the phone screen interview given to all potential participants, potential control group participants were administered the SCID-I screener for Axis I pathology (First et al., 2002) in addition to a brief clinical interview. If volunteers were determined eligible to participate in the study, an appointment time was scheduled.

Upon arriving at the Cardiac Neuroscience Laboratory at Rutgers University, eligible volunteers were asked to provide written informed consent. Once informed consent was obtained, control group volunteers completed the SCID-II screener to screen for personality disorder pathology. Relevant sections of the SCID-II interview were administered if necessary to rule out personality disorders. BPD group volunteers coming from treatment sites other than DBT-RU were also administered the SCID-II screener (volunteers from DBT-RU complete the SCID-II screener during admission to DBT-RU). Volunteers found to be ineligible for any reason were compensated at a prorated amount of \$10 per hour.

All eligible participants then completed the psychosocial questionnaire battery that took approximately 45 minutes. After completing questionnaires, participants were seated in a comfortable chair located 2.5 meters in front of a large computer screen in a sound attenuated, dimly lit room. Dermal ECG electrodes were placed laterally below the deltoid muscles on the right and left arms, as well as in a lateral position above the left ankle. A respiration belt was placed across the chest to capture thoracic breathing. Continuous blood pressure was measured using a cuff attached to the middle finger on the right hand. Electrodermal activity was measured using two stainless steel electrodes affixed to the thenar eminence and hypothenar eminence of the palm of the right hand.

Participants first performed a standardized low-demand “vanilla” task (Jennings et al., 1992) for 6 minutes, wherein they viewed colored rectangles on a computer screen while silently counting the number of blue rectangles. This procedure provided the basal HRV measures for the study. Following this, participants viewed 36 pictures from the BPD

IAPS picture set for a total of 6 minutes. During this task participants viewed each image for 5 seconds (order counterbalanced), followed by 5 seconds of black screen at which time they verbally reported their subjective arousal to each image using the Self-assessment Manikin, a standardized 9-point Likert scale, where 1 represents lowest arousal, and 9 represents greatest arousal (Lang, Bradley, & Cuthbert, 2001). Immediately following the picture set presentation, participants engaged in a 6-minute post-stressor recording period where they were asked to sit still while their physiology was recorded. In order to reflect a ‘real life’ post-stressor recovery period, no specific instructions were given during this task. Following this, both groups again engaged in the standardized low-demand “vanilla” task for 6 minutes. The entire HRV recording procedure took approximately 30 minutes, and was administered by the principal investigator, and a post-baccalaureate research assistant.

Analysis of Heart Rate, Blood Pressure Variability, and Skin Conductance Variance

HRV is defined as changes in time interval from R-spike to R-spike (RR) in an ECG signal, where the R-spike represents a single contraction of the heart’s ventricles. Changes in the RR interval capture moment-to-moment, fine-grained perturbations in the heart’s rhythm that reflect subtle changes in the central and autonomic nervous systems. This may be analyzed in a number of different ways. For example, time domain indices are derived from direct measurement of sequential RR intervals obtained from the ECG signal with manual corrections for artifacts and irregular beats, also referred to as normal-to-normal (NN) intervals:

$$\overline{RR} = \frac{RR_1 + RR_2 \dots R_N}{N} = \frac{1}{N} \sum_{i=1}^N RR_i [ms; -, ms]$$

The standard deviation of all NN intervals (SDNN) is a commonly utilized time domain index used to gauge general autonomic regulatory activity.

$$SDNN = \sqrt{\frac{1}{N} \sum_{i=1}^N (RR_i - \overline{RR})^2} [ms; -, ms]$$

In addition, the root of the mean squared differences of successive NN intervals (RMSSD), as well as the number of pairs of adjacent NN intervals differing by more than 50ms throughout a recording (NN50), which is typically expressed as the percentage of NN50 count divided by the total number of NN intervals (pNN50), closely reflect parasympathetic vagal activity (Task Force, 1996). SDNN and RMSSD are expressed in milliseconds (ms), while pNN50 is expressed as a percentage.

$$RMSSD = \sqrt{\frac{1}{N-1} \sum_{i=1}^{N-1} (RR_{i+1} - RR_i)^2} [ms; -, ms, ms]$$

$$NN50 = \sum_{i=1}^N \{ |RR_{i+1} - RR_i| > 50_{ms} \} [count; -]$$

$$pNN50 = \frac{NN50}{N} \cdot 100 [\%; -]$$

Alternatively, HRV may be assessed in the frequency domain using power spectral density analysis, which provides information about how power distributes as a function of frequency (Task Force, 1996). By convention, frequency domain indices are divided into high frequency (HF: 0.15-0.4 Hz), low frequency (LF: 0.04-0.15 Hz), and very low frequency (VLF: 0.005-0.04 Hz) domains. HF HRV activity is primarily parasympathetically mediated by vagal activity (Berntson et al., 1997; Task Force, 1996). HF HRV is the most widely

studied aspect of HRV because it captures fine-grained changes in parasympathetic activation. Of the spectral HRV indices, it is most indicative of a well-functioning ANS and general health, and is commonly affected in cases of pathology (e.g., Appelhans & Luecken, 2006; Eddie, 2012; Hughes & Stoney, 2000). LF HRV reflects both parasympathetic and sympathetic influences, such that it captures the dual action of the baroreflex system as it affects both HRV and vascular tone (Cevese, Gulli, Polati, Gottin, & Grasso, 2001; Vaschillo et al., 2011). Finally, though not well understood, VLF HRV is thought to reflect fluctuations in the ANS (Berntson et al., 1997) that mediate baroreflex control of vascular tone (Vaschillo et al., 2011). Spectral indices are expressed as ms^2 .

Blood pressure characterizes pressure exerted on arterial walls by ventricular ejection of blood from the heart, and is commonly expressed as systolic arterial blood pressure (SAP; arterial pressure during systolic contraction of the heart) and diastolic arterial blood pressure (DAP; arterial pressure during ventricular relaxation between heart contractions). Derived from the vascular pressure waveform, measures of BPV characterize baroreflex mediated moment-to-moment changes in SAP and DAP that are indicative of autonomic flexibility and adaptability (Vaschillo et al., 2011; Voss, Boettger, Schulz, Gross, & Bär, 2011). Blood pressure variability is expressed in the present investigation as the standard deviation of systolic blood pressure (SAPD), and the standard deviation diastolic blood pressure (DAPD). Overall blood pressure may be expressed by mean arterial pressure (MAP; the average blood pressure of an individual that considers both SAP and DAP), and its standard deviation (MAPD; Parati et al., 2001). All BP indices are expressed in millimeters of mercury (mmHg).

$$SAPD = \sqrt{\frac{\sum (SAP - \overline{SAP})^2}{N - 1}}$$

$$DAPD = \sqrt{\frac{\sum (DAP - \overline{DAP})^2}{N - 1}}$$

$$MAPD = \sqrt{\frac{\sum \left([DAP + \frac{1}{3}\{SAP-DAP\}] - \overline{[DAP + \frac{1}{3}\{SAP-DAP\}]} \right)^2}{N - 1}}$$

Skin conductance measures, which reflect sympathetically mediated fluctuations in sweat gland activity are widely used physiological indicants of affective processing and responding (Boucsein, 2012, p. 3-7; M. E. Dawson, Schell, & Filion, 2007) that are especially sensitive to aversive stimulation and perceived threat (Fowles, 1988). Here SC is expressed as the standard deviation of SC measured in milliseconds, referred throughout this dissertation as SVC. Because sweat gland activity also reflects thermoregulatory processes (Bini, Hagbarth, Hynninen, & Wallin, 1980), low frequency changes in raw SC that reflect slow responses to ambient temperature (0.01 – 15Hz) were filtered out prior to the calculation of SCV. Notably, because SC measures reflect sympathetically mediated fluctuations in sweat gland activity, lack of perspiration, or sweat gland saturation can reduce the sensitivity of these measures. SCV is expressed in microseconds (μ S).

$$SCV = \sqrt{\frac{\sum (SC - \overline{SC})^2}{N - 1}}$$

Respiration measures were calculated from the thoracic respiration record and are expressed as breathing frequency in hertz (Hz), and tidal volume in milliliters (ml).

Analysis

Data Distribution and Outlier Analyses

Preliminary visual inspection and univariate analysis were used to check for normality for each psychological measure. Variables that with skew or kurtosis >1 were subjected to logarithmic transformation (i.e., logarithm/reflect and logarithm).

Mahalanobis distance was used to detect multivariate outliers (de Maesschalck, Jouan-Rimbaud, & Massart, 2000).

Associations Between Anxiety and Depression, and Baseline Physiological Measures

Anticipated associations between trait anxiety and depression, and baseline physiological indices within the BPD group were examined using Pearson's correlation coefficients.

A Priori Hypothesis Testing

A priori hypotheses were tested using repeated measures mixed models with unstructured covariance matrix (Wolfinger & Chang, 1995) to examine the effect of group (BPD, control), experimental task (baseline, cue exposure, recovery period), and their interaction on target physiological indices including HR, SDNN, HF HRV, LF HRV, SAPD, and SCV, with model level Bonferroni correction (6 tests, $\alpha' = .008$) to control for alpha level inflation. To check for possible respiration effects on HRV, these models were also tested with respiration frequency included as a covariate.

Main effects of group are indicative of differences between the BPD and control groups on target physiological measures across experimental tasks. Main effects of time are indicative of change from baseline to cue reactivity, from cue reactivity to the recovery

period, and from baseline to the recovery period on each target index, in the combined groups. The group \times time interaction effects were indicative of whether the groups differed in the way they changed from baseline to cue reactivity, and from cue reactivity to the recovery period, on each of the target physiological indices. When indicated by significant main or interactions effects, post hoc least square means difference tests were conducted.

Tests for Effects of Substance Use in Participants with Borderline Personality Disorder

Within the BPD group, the effects of chronic substance use on baseline physiology, change in physiology in response to cue exposure, and change in physiology from cue exposure to the recovery period were assessed. To test this, two sets of residual change scores were derived by regressing HR, SDNN, HF HRV, LF HRV, SAPD, and SCV scores during cue exposure onto their respective scores during baseline, and by regressing post-cue exposure recovery period scores onto their respective measure during cue exposure.

Residuals represent the error in the regression model and are calculated by subtracting the model's predicted values from the observed values (i.e., $e = y - \hat{y}$), and are preferable to utilizing raw change scores because they account for effects of regression to the mean.

Residual scores were subsequently tested for association with substance use measures using general linear models.

Exploratory Analyses

Post Cue Exposure Recovery Latency

A more fine-grained analysis of latency of recovery from cue exposure was accomplished by separating the recovery period into a first and a second 3-minute interval. Mixed models for HR, SDNN, HF HRV, LF HRV, SAPD, and SCV were used to examine

between group differences in change in from cue exposure, to the first and second halves of the recovery period, with model level Bonferroni correction (6 tests, $\alpha' = .008$) to control for alpha level inflation.

Dissociative Tendencies as a Moderator of Psychophysiological Cue Reactivity

Previous work has shown individuals with BPD who report high levels of state dissociative tendencies tend to be less psychophysiologicaly responsive to startle (Ebner-Priemer et al., 2005; Ebner-Priemer et al., 2009). As such, in participants with BPD, dissociative tendencies measured by the DES-II, were posited to moderate the relationship between psychophysiological indices at baseline and during cue exposure. Partial least squares path modeling (Henseler & Fassott, 2010) was employed to parse out the possible effects of trait dissociation on cue reactivity, by regressing covaried baseline HR, SDNN, pNN50, HF HRV, LF HRV, SAP, SAPD, or SCV (exogenous variable), continuous DES-II score (moderator variable), and HR, SDNN, pNN50, HF HRV, LF HRV, SAP, SAPD, or SCV \times DES-II score (interaction term), onto HR, SDNN, pNN50, HF HRV, LF HRV, SAP, SAPD, or SCV during cue exposure (endogenous variable).

Expression of Effect Sizes

For consistency, effect sizes were expressed as Cohen's d throughout, with $d = .20$ interpreted as a small effect, $d = .30$ interpreted as a medium effect, and $d = .50$ interpreted as a large effect (J. Cohen, 1988). Effect sizes for means tests were calculated using Cohen's standard formula (J. Cohen, 1988, p. 274). For regression analyses, eta-squared effect sizes were converted to d per Cohen's algorithm (1988, p. 281), while for correlation analyses,

Pearson's r was converted to d using Rosenthal's formula (R. Rosenthal, 1994, p. 239). For chi-square analyses, χ^2 was converted to d per Ellis' formula (Ellis, 2015).

Results

Data Distribution and Outlier Analyses

Variables including SDNN, RMSSD, HF HRV, LF HRV, VLF HRV, and SCV were excessively skewed or kurtotic and were thus logarithmically transformed. The remaining physiological indices, HR and pNN50, did not require transformation.

The Mahalanobis distance test detected one multivariate outlier in the baseline task (a BPD group participant), and one outlier in the recovery period task (a control group participant). These participants were subsequently excluded from analyses involving baseline and/or recovery period physiological measures, respectively. A separate test for multivariate outliers using the change scores from baseline to cue exposure, and cue exposure to recovery period did not reveal any outliers.

Sample Characteristics

Groups did not differ significantly on sex, age, and body mass index (all $p > .05$; see Table 1). In the BPD group, 16 participants identified as White/European American, 2 as Asian, and 4 as other/mixed race. In the control group, 16 participants identified as White/European American, 5 as Asian, and 1 as other/mixed race.

Participants with BPD reported significantly more lifetime months of therapy (see Table 1). Modal income for participants with BPD was $< \$15,000$, while the modal income for controls was bifurcated between two income brackets, $< \$15,000$, and $> \$90,000$. In the BPD group, 4 participants were married, 17 had never been married, 1 was divorced, and 1

was separated, while in the control group, 5 participants were married, 16 had never married, and 1 was widowed.

Characterization of BPD Group Participant Psychiatric Comorbidity

As anticipated, participants with BPD exhibited a high degree of psychiatric comorbidity. Nineteen of 22 participants had a co-occurring psychological diagnosis or diagnoses. The count of various DSM-IV-TR Axis I diagnoses were as follows: 11 major depressive disorder, 10 generalized anxiety disorder, 7 panic disorder, 7 social anxiety disorder, 5 bipolar disorder (4 type II, and 1 type I), 4 post-traumatic stress disorder, 4 obsessive compulsive disorder, 4 eating disorder not otherwise specified, 2 anxiety disorder not otherwise specified, 2 specific phobia, 2 body dysmorphic disorder, 1 bulimia nervosa, 1 hypochondriasis, 1 somatization disorder, and 1 agoraphobia.

There was also considerable personality disorder comorbidity. The count was as follows: 4 avoidant personality disorder, 2 obsessive compulsive personality disorder, 2 dependent personality disorder, 2 paranoid personality disorder, 1 antisocial personality disorder, and 1 histrionic personality disorder.

Participant Medications

Fourteen of 22 participants in the BPD reported current use of prescribed medications that could potentially affect psychophysiological measures, including 7 participants taking an antipsychotic or mood stabilizers (i.e., aripiprazole, lithium, lurasidone, olanzapine, risperidone), 4 taking a benzodiazepines (i.e., alprazolam, clonazepam), 3 taking a non-benzodiazepine anxiolytic or sleep aid (i.e., buspirone, zolpidem), 6 taking a selective serotonin reuptake inhibitor (i.e., citalopram, escitalopram,

fluoxetine, sertraline), 3 taking a serotonin agonist / reuptake inhibitors (i.e., trazodone), 1 taking bupropion, and 2 taking a stimulant for ADHD (i.e., lisdexamfetamine, methylphenidate).

Control group participants reported no medications that are known to affect physiological measures.

Preliminary Between-group Psychosocial Comparisons

Between groups comparisons of self-reported psychosocial measures are reported in Table 2. As predicted, participants with BPD, compared to healthy controls, reported greater state and trait anxiety (STAI-Y scores), greater depression (BDI scores), more present moment negative affect (PANAS scores), greater emotion dysregulation (DERS and AAQ-II scores), and greater dissociative symptomology (DES-II scores). Contrary to hypotheses though, groups were not different in terms of present moment positive affect as measured by the PANAS.

Groups did not differ in terms of frequency of past year exercise, or average length of exercise sessions ($p > .05$). Groups did differ, however, on sleep measures. Participants with BPD reported significantly more trouble initiating sleep and falling back to sleep compared to controls, $\chi^2 (1, N = 44) = 11.2, p < .05, d = 1.17$, although ultimately the groups did not differ on average hours of sleep per night ($p > .05$).

Substance Use

As predicted, the BPD group had higher rates of lifetime alcohol and other drug dependence (see Table 3 & 4), however, contrary to predictions, groups were not different

in terms of past month and past year drinking behaviors (see Table 3), or drug use behaviors aside from nicotine (see Table 4).

One BPD participant was in recovery from alcohol dependence and was abstinent from alcohol in the past year, and 3 control participants endorsed trying alcohol, but never becoming drinkers. For individuals in each group that endorsed drinking in the past year, results showed that BPD and control group participants initiated drinking at a similar age, had a similar number of drinking days in a typical week in the past month, drank similar quantities in the past month, and were similar in terms of drinking during their heaviest drinking week in the past month. Additionally, a non-significant chi-square test ($p > .05$) indicated groups drank at similar frequencies in the past year.

Participants in the BPD group used nicotine more frequently in the past month and past year compared to participants in the control group (see Table 4).

The groups, however, were similar in terms of their use of drugs other than alcohol or nicotine. There were no between group differences in frequency of drug use in the past month (measured as number of days of use in the past month) or frequency of drug use over the past year (measured as average times using per week during the past year) for amphetamines, cannabis, cocaine, or opiates (see Table 4). Notably, for these drug classes, both groups reported very little past month and past year use.

Subjective Arousal to Emotionally Evocative Pictures

As predicted, participants with BPD reported significantly more subjective arousal to emotionally evocative pictures during the cue exposure component of the experimental session, $t(42) = 2.03$, $p < .05$, $d = .63$, scoring an average arousal rating of 5.02 ($SD = 1.33$),

with a total arousal rating of 180.8 ($SD = 47.9$), while control group participants scored an average arousal rating of 4.21 ($SD = 1.33$), and a total arousal rating of 151.5 ($SD = 47.9$).

Within the BPD group, BPD severity, as measured by the combined standardized scores of the Borderline Symptom List and Difficulties in Emotion Regulation Scale, was not significantly associated with mean subjective arousal, $p > .05$.

Associations Between Anxiety and Depression, and Baseline Physiological Measures

The hypothesis that trait anxiety and depression would be negatively associated with parasympathetically mediated HRV within the BPD group was partially supported.

Trait anxiety (total STAI-Y trait score) was negatively associated with pNN50, $r(19) = -.46$, $p < .05$, $d = 1.04$, while directionally concordant large effect sizes that did not reach statistical significance were observed for SDNN, $r(19) = -.43$, $p = .05$, $d = .95$, RMSSD, $r(19) = -.43$, $p = .05$, $d = .95$, and HF HRV, $r(19) = -.38$, $p > .05$, $d = .82$. Depression (total BDI score), however, was not associated with HRV.

A Priori Hypotheses Tests

Hypothesis 1, that relative to controls, participants with BPD would show lower baseline levels of parasympathetically mediated neurocardiac flexibility and greater sympathetic activation was partially supported. Participants with BPD did exhibit greater HR and SCV at resting baseline, however, groups were not significantly different on other measures reflecting neurocardiac flexibility including SDNN, RMSSD, pNN50, HF HRV, LF HRV, and SAPD (Table 5). Further, groups were similar on measures of respiration (Table 5).

Hypothesis 2, that participants with BPD would report greater subjective arousal than controls, but that both groups would exhibit similar parasympathetic withdrawal and increased sympathetic activation in response to cue exposure, was partially supported. Participants with BPD reported greater subjective arousal to the picture stimuli. In addition, as shown by a main effect of time (Table 6) and subsequent post hoc least square means tests (Table 7), the combined groups demonstrated increased sympathetic activation from baseline to cue exposure as evinced by an increase in SCV. Similarly, both groups also demonstrated an increase in HR in response to cue exposure, which may be indicative of increased sympathetic activation, decreased parasympathetic activation, or a combination of both. The combined groups also demonstrated an increase in SDNN from cue exposure to cue recovery period, although after respiration frequency was included as model covariate, this effect was no longer statistically significant. Overall, however, there was no significant change in parasympathetic activation in response to cue exposure, as indicated by a null main effect for HF HRV.

Hypothesis 3, that during the post-cue exposure recovery period participants with BPD would show continued parasympathetic withdrawal and sympathetic activation, while the control group would return to their pre-challenge physiological baseline, was not supported. Contrary to predictions, no interaction effects were observed on any target physiological index, suggesting groups did not differ in their physiological change between these tasks. A main effect of time, however, indicated that the combined groups demonstrated a decrease in SCV from cue exposure to the post-cue exposure recovery period (Table 7).

A Posteriori Hypothesis Tests

Because of BPD's complex polythetic presentation, and the varying degrees of severity among individuals meeting diagnostic criteria for BPD (Crowell, Beauchaine, & Linehan, 2009; Gunderson & Links, 2009), BPD severity had been highlighted a priori as a potential factor to consider in the present analyses, though no specific hypotheses were made. With this in mind, it was thus tentatively hypothesized that individual differences in BPD severity may be driving the observed null effects for cue exposure recovery on target physiological measures. To more fully characterize the potential effects of BPD severity on responses to emotional stimuli, the potential moderating effects of BPD severity on cue reactivity were also tested.

To do this, first a measure of BPD severity was calculated by combining individuals' standardized total scores (z -scores) on the BSL-23 and DERS, two correlated measures ($r = .77$, $p < .05$, $d = 2.41$) reflecting BPD symptomology (standardized total scores were used to give the two questionnaires equal weighting). Then, BPD severity scores were regressed onto residualized physiological change scores (previously derived by regressing HR, SDNN, HF HRV, LF HRV, SAPD, and SCV scores during cue exposure onto their respective measure during baseline, and by regressing recovery period scores onto their respective measure during cue exposure). To more fully characterize the potential role of parasympathetic factors, pNN50 and RMSSD scores were also included in these a posteriori analyses because, like HF HRV, they are understood to reflect parasympathetic tone.

The a posteriori hypothesis was supported. In terms of physiological change from cue exposure to recovery period, lower BPD severity within the BPD group predicted significant decreases in RMSSD, pNN50, and HF HRV from cue exposure to the recovery period, while higher BPD severity scores predicted significant increases in RMSSD, pNN50, and HF HRV (Table 8 & Figure 2). In addition, SDNN evinced a large effect size trend that was directionally concordant with results for RMSSD, pNN50, and HF HRV.

With regard to physiological change from baseline to cue exposure, within the BPD group, BPD severity was negatively associated with pNN50, such that lower BPD severity predicted increases in pNN50 from baseline to cue exposure, while greater BPD severity predicted decreases in pNN50 from baseline to cue exposure (Table 8 & Figure 1). Large effect sizes following the same directional pattern were observed for SDNN, RMSSD, HF HRV, and LF HRV, though these results did not reach statistical significance (Table 8 & Figure 1).

Mean HR also evinced a large, but non-significant effect size, trending in the opposite direction (Table 8 & Figure 1). Specifically, lower BPD severity predicted decreases in HR from baseline to cue exposure, while greater BPD severity predicted increases in HR from baseline to cue exposure.

Similarly, a large, but non-significant effect size was observed for SCV, such that greater BPD severity was associated with increases in SCV from baseline to cue exposure (Table 8). Careful slope inspection, however, indicated the majority of participants (16 of 22) showed slight to moderate reductions in SCV from baseline to cue exposure.

Respiration frequency was not correlated with BPD severity, or any physiological measure change score, suggesting participants' respiration did not influence these results.

Tests for Effects of Substance Use in Participants with Borderline Personality Disorder

The low numbers of participants with BPD endorsing past month, and past year amphetamine, cannabis, cocaine, opiate, and nicotine use, as well as lifetime histories of alcohol and other drug dependence, precluded analysis for these measures. As such, tests for the effects of substance use in participants with BPD focused on past month and past year alcohol use.

The hypothesis that frequency of past month and past year alcohol use, as well as quantity of alcohol consumed in a typical week in the past month would be negatively associated with basal levels of target HRV measures in the BPD sample, was not supported, all $p > .05$.

The hypothesis that substance use would predict cue exposure response, specifically that greater past month and past year substance use would predict greater autonomic responses to emotionally evocative pictures, was not supported. All analyses for associations between alcohol use and change in physiology from baseline to cue exposure were non-significant, $p > .05$.

Hypothesis 4, that greater substance use would predict less autonomic recovery after perturbation was partially supported. Quantity of alcohol consumed in a typical week in the past month was negatively associated with change in SAPD, $F(1, 20) = 5.53$, $p < .05$, $d = 1.05$. Slope inspection revealed that greater alcohol use predicted either decreases, or very small increases in SAPD from cue exposure to the recovery period, while those who

drank less or not at all were more likely to experience larger increases in SAPD. All other analyses for associations between past month and past year alcohol use and change in physiology from cue exposure to the recovery period were non-significant, $p > .05$.

Post Cue Exposure Recovery Latency Analysis

An exploratory analysis of latency of recovery from cue exposure was carried out by separating the recovery period into a first and a second 3-minute interval. Mixed models for HR, SDNN, HF HRV, LF HRV, SAPD, and SCV were used to examine between group differences in change in from cue exposure, to the first and second halves of the recovery period. Analyses did not produce any significant interaction effects, all $p > .05$, suggesting groups did not differ in terms of their temporal patterns of recovery.

Dissociative Tendencies as a Moderator of Psychophysiological Cue Reactivity

Partial least squares path modeling was used to test if dissociative tendencies—measured by participants' total score on the DES-II—moderate psychophysiological cue reactivity. Results indicated a significant moderating effect of dissociative tendencies on pNN50, $\beta = -0.4$, $SE = 0.0$, $z = -4.3$, $p < .05$, and SAPD, $\beta = 1.3$, $SE = 0.0$, $z = 3.2$, $p < .05$. Slope inspection showed that greater trait dissociation reflected by total DES-II scores predicted decreases in pNN50 from baseline to cue exposure, while lower levels of trait dissociation predicted increases in this HRV index. Slope inspection also revealed that greater trait dissociation was associated with increases or little change in SAPD from baseline to cue exposure, while lower trait dissociation predicted decreases in SAPD. Moderation effects for HR, SDNN, HF HRV, LF HRV, and SAP did not reach statistical

significance. Including respiration frequency as a covariate in the models did not affect these results.

Checks for Effects of Medication, Time in Treatment, and Age on Physiological Measures

T-tests showed participants in the BPD group taking medication were not different from those not taking medication on physiological measures at baseline, during cue exposure, or during the recovery period, all $p > .05$. Further, initial results for between group differences in baseline physiology were not changed by removing BPD participants on medication, or not on medication, from the analysis. Similarly, the results of the a priori hypothesis tests were not affected by excluding BPD participants on medication, or not on medication, from the analysis.

For participants with BPD, general linear models showed that time in Dialectical Behavior Therapy and total lifetime psychological treatment were not associated with basal levels of physiology, nor were they predicted by BPD severity, all $p > .05$.

In the combined sample, participant age predicted SDNN, $F(1, 41) = 7.47$, $p < .05$, $d = 0.85$, however, all other associations between age and physiological indices at baseline were non-significant, $p > .05$. Adding age to the a priori hypothesis tests models did not change their results.

Discussion

BPD is a complex psychiatric condition characterized by intense and rapidly shifting emotional states, impulsivity, and instability in self-image (Glenn & Klonsky, 2009). Its sequelae include intense feelings of emptiness, shame, loneliness, panic, and rage, which lead to behaviors such as substance misuse, non-suicidal self-injury, and suicide

(Gunderson & Links, 2009; Leichsenring et al., 2011). To date, the cognitive components of emotion dysregulation in BPD have received much research attention. The collateral psychophysiological processes, however, remain poorly understood. Because emotion regulation is mediated by both cognitive and physiological processes (Benarroch, 1997; Hagemann et al., 2003), this knowledge gap may be limiting progress in the treatment of BPD. As such, this investigation sought to comprehensively assess psychophysiological differences between individuals with BPD and controls, and examine whether a loss of flexibility in fundamental ANS processes may contribute to the emotion dysregulation observed in BPD. To accomplish this, psychophysiological differences between individuals with BPD and healthy controls were assessed at rest, during exposure to emotionally evocative images, and during a post cue exposure recovery period. Additionally, because substance use disorders are highly comorbid with BPD, and may interact with and exacerbate BPD pathology (Axelrod et al., 2011; Dimeff et al., 2000; Kruegelbach et al., 1993), this study also investigated the effects of co-occurring substance use on psychophysiological processes in individuals with BPD.

As hypothesized, between group psychophysiological differences were observed at baseline showing greater HR and SCV in participants with BPD, compared to controls, however, contrary to predictions, there were no significant between group differences in HRV at baseline. Main effects of group and time were found in response to, as well as in recovery from exposure to emotionally evocative images on HR and SCV, while a main effect of time was observed for SDNN. Specifically, the main effects of group indicated participants with BPD had greater HR and SCV when all three tasks were considered

together. A main effect of time for HR, SDNN, and SCV, and subsequent post hoc analyses showed the combined groups demonstrated increases in HR and SCV in response to exposure to emotionally evocative images, a decrease in SCV during recovery from image exposure, and an increase in SDNN from baseline to the recovery period. No group \times time interaction effects were observed, suggesting the groups were not different in terms of how they responded to or recovered from exposure to emotionally evocative stimuli. This was in spite of the fact that participants with BPD rated the images as subjectively more arousing than controls. The absence of observed interaction effects led to speculation that BPD symptom severity may be influencing results. This postulate was supported by a posteriori analyses, which found that within the BPD group, BPD severity moderated physiological response to, as well as recovery from exposure to emotionally evocative images.

Associations between physiological measures and substance use behaviors were also investigated within the BPD group. Contrary to expectations, however, participants with BPD generally reported relatively low levels of substance use, and fewer than expected participants had lifetime histories of substance dependence. This precluded the planned, in-depth analyses, although associations between alcohol use and physiology were investigated. Hypotheses about the effects of alcohol on physiology in participants with BPD, however, were largely unsupported.

Preliminary Between-group Psychosocial Comparisons

As anticipated, participants with BPD, compared to controls, reported greater state and trait anxiety, greater depression, more present moment negative affect, greater emotion dysregulation, greater dissociative symptomology, and more difficulty initiating sleep and

falling back to sleep. This is in line with a large literature showing individuals with BPD experience higher rates of problems in these areas than non-clinical samples (see Leichsenring et al., 2011 for review).

Contrary to hypotheses, groups were not different in terms of present moment positive affect, as measured by the PANAS. Though this finding ran contrary to what was hypothesized, it is not without precedent. Levine et al. (1997) also found that individuals with BPD experience greater negative affect to non-psychiatric controls, but similar levels of positive affect. Although negative affect, per se, is not a diagnostic marker of BPD in either the DSM-IV-TR (American Psychiatric Association, 2000) or ICD-10 (World Health Organisation, 1992) classifications, heightened negative affect, and not reduced positive affect, may be an important marker of BPD pathology, especially considering negative affect is positively associated with BPD traits and features (Cheavens et al., 2005; M. Z. Rosenthal, Cheavens, Lejuez, & Lynch, 2005).

Substance Use

Participants with BPD were more likely to have a lifetime diagnosis of alcohol and other drug dependence, however, contrary to predictions, groups were not different in terms of past month and past year alcohol or other drug use behaviors, aside from nicotine. The low rates of substance use in the present sample was surprising given the usually high rates of substance use in individuals with BPD (Trull et al., 2000). This may be explained by the fact that all study participants with BPD were receiving Dialectical Behavior Therapy at the time of their participation in the present investigation. In most instances, patients engaged in Dialectical Behavior Therapy for BPD who also have co-occurring substance use

problems are encouraged or required to stop substance use while in treatment, as this behavior typically interferes with treatment goals and precludes reliance on more effective, skill-based coping strategies (Linehan, 1993, 2014). It is therefore possible that in the present sample, the relatively low rates of substance use in participants with BPD may be accounted for by their active participation in treatment.

The fact, however, that participants with BPD reported similar substance use to controls in the past year runs contrary to this postulate. Though it is possible they were engaged in other therapies prior to beginning Dialectical Behavior Therapy, on average, participants with BPD had only received an average of approximately three months of lifetime Dialectical Behavior Therapy at the time they participated in the study.

Subjective Arousal to Emotionally Evocative Pictures

As anticipated, participants with BPD reported significantly more subjective arousal to emotionally evocative pictures during the cue exposure component of the study. The difference between the BPD and control groups was, however, not especially robust, as evinced by a small effect size difference in arousal ratings. This relatively small effect size difference and the lack of a relationship between subjective arousal and BPD severity within the BPD group, suggests images depicting interpersonal and social content taken from the IAPS may not sufficiently target BPD sensitivities at a level of intensity that is optimal for BPD cue reactivity studies. For instance, images depicting abandonment, non-suicidal self-injury, and suicide do not feature heavily in the IAPS and thus were not well represented in the set formed in Sloan et al.'s (2010) study. This suggests that the development of an effective BPD specific picture set may require the collection and

validation of a corps of novel images that closely focus on key BPD themes such as frantic efforts to avoid abandonment, unstable interpersonal relationships, transient dissociative episodes, non-suicidal self-injury, and suicide.

Associations Between Anxiety and Depression, and Baseline Physiological Measures

Previous investigations have shown trait anxiety and depression are inversely related to indices of HRV characterizing resting parasympathetic activation (e.g., Chang et al., 2012; Eddie, 2012; Miu et al., 2009). As such, within the BPD group, greater levels of trait anxiety and depression were expected to predict lower basal levels of pNN50, RMSSD, and HF HRV. This postulate was partially supported.

In participants with BPD, trait anxiety was significantly negatively associated with pNN50. Parallel large effect size associations were observed between anxiety and SDNN, RMSSD, and HF HRV, although these did not reach statistical significance. This is in line with psychophysiological perspectives on anxiety, which hold that chronic anxiety is related to a loss of biobehavioral flexibility reflected in, or resulting from a loss of vagal tone (Friedman & Thayer, 1998; Thayer et al., 1996; Thayer & Lane, 2000).

Contrary to predictions, however, depression did not predict HRV in the present BPD sample. Notably, the majority of studies investigating the relationship between depression and HRV have studied individuals with primary depressive disorders, with little or no psychiatric comorbidity. These populations are different from the present sample of individuals who have a primary diagnosis of BPD. It is possible that there are differences in autonomic system involvement in primary depressive disorders and depression occurring secondary to BPD or other mental disorders. Future studies should investigate these

potential differences, by comparing individuals with primary depressive disorders and individuals with secondary depressive disorders on psychophysiological measures.

A Priori Hypotheses Tests

Hypothesis 1 predicted that relative to controls, participants with BPD would show lower baseline levels of HRV, and greater sympathetic activation. This was partially supported. Participants with BPD did exhibit greater HR and SCV at resting baseline, however, groups were not significantly different at resting baseline on measures of HRV, or SAPD.

This finding is concordant with Ebner-Priemer et al.'s (2007) observation of greater resting HR in individuals with BPD compared to healthy controls, as well as Ebner-Priemer et al. (2007), Austin et al.'s (2007), and Gratz et al.'s (2011) null finding for between group differences in resting HRV. It is also consistent with Kuo and Linehan's (2009) observation of greater resting levels of skin conductance response in individuals with BPD. The current findings are, however, discordant with results published by Weinberg et al. (2009), and Kuo and Linehan (2009), who observed lower resting levels of parasympathetically mediated HRV in individuals with BPD, compared to healthy controls.

The heterogeneity of the samples utilized in these investigations may explain some of the divergent findings across studies. Further, though this investigation recruited a naturalistic sample that minimized and/or controlled for potential confounds associated with participant age, time in treatment, diagnosis of BPD, medication, and psychiatric comorbidity, some of these factors may have nevertheless influenced results.

For instance, psychiatric comorbidity is typical in BPD samples, and may influence psychophysiology in unpredicted ways. While excluding study volunteers with comorbid disorders may seem prudent, omitting such individuals can reduce ecological validity by inadvertently excluding people with more severe BPD who commonly have affective disorders secondary to BPD (Comtois, Cowley, Dunner, & Roy-Byrne, 1999). Thus, whether including or excluding co-occurring mental disorders, comorbidity remains a key issue that bears consideration whenever interpreting psychophysiological results in studies of BPD.

As previously noted, medications can also affect physiology, and may in part account for the equivocal findings in differences in basal HRV between individuals with BPD and controls across the studies reviewed here, and the present investigation. Notably however, checks for effects of medication in the present study showed no differences in psychophysiology between BPD participants taking medication and those not taking medication. Further, results for between group differences in baseline psychophysiology and results of the a priori hypotheses tests were not affected by including or excluding BPD participants on medication, or not on medication.

While ideally studies such as this would utilize samples free of medication, excluding volunteers because of medication also threatens ecological validity as participants with greater BPD severity are also most likely to be on medication (Sansone et al., 2003). The present investigation anticipated this problem and included individuals on medications, while making marked efforts to reduce potential effects of medication by selectively excluding volunteers taking certain pharmaceuticals known to directly affect the

cardiovascular system, and strategically scheduling session times to reduce acute medication effects. This factor, nevertheless, could have influenced results.

Another possible explanation for these equivocal findings is participant BPD severity, both within samples and between studies. As discussed below, BPD severity had a moderating effect on response to, and recovery from emotionally evocative images in the present sample. This finding speaks to the possibility that within sample differences in BPD severity may have undermined tests for between group differences in basal physiology, although null associations between BPD severity and basal physiology within the BPD group suggest otherwise.

Future studies will ideally utilize large samples so that possible moderating effects of psychiatric comorbidity, medication, and BPD severity on ANS processes can be parsed out. Larger samples will afford strategies such as within group tests for moderation, as well as assessment of physiological differences between individuals with psychiatric comorbidity versus no psychiatric comorbidity, more versus less severe BPD, and those on medication versus those not on medication.

Hypothesis 2, predicted that compared to controls, participants with BPD would report greater subjective arousal to the emotionally evocative images, while both groups would exhibit similar reductions in parasympathetic tone, and increased sympathetic activation in response to the images. This hypothesis was partially supported. Participants with BPD reported greater subjective arousal to the picture stimuli. Further, consistent with findings by Weinberg and colleagues (2009) who challenged volunteers with a social stressor, both groups demonstrated increased sympathetic activation from baseline to cue

exposure as evinced by an increase in SCV. Similarly, both BPD and control groups also demonstrated an increase in HR in response to cue exposure, which may be an effect of increased sympathetic activation, decreased parasympathetic activation, or a combination of both. Overall, however, consistent with Weinberg et al.'s findings, there was no significant change in parasympathetic activation in response to cue exposure in either group. These results suggest groups were similar in their response to emotionally evocative images in that they both demonstrated increases in sympathetic activation, but no significant changes in parasympathetic tone.

A posteriori analyses, however, highlighted an important factor not considered in previous studies. Within the BPD group, BPD severity moderated cue reactivity, such that participants with greater BPD severity tended to show decreases in HRV and SCV in response to cue exposure, while individuals with lower BPD severity tended to show increases in HRV. This is a key finding as it demonstrates for the first time differing patterns of psychophysiological responding to emotional stimuli within a group of people with BPD. Specifically, individuals with lower BPD severity were shown to exhibit physiological responses similar to controls, whereas individuals with higher BPD severity exhibited the opposite response.

This finding shares important commonalities with Gratz et al. (2013) who observed that participants with co-occurring BPD and AVPD demonstrated decreases in HRV in response a distress tolerance task, while participants with BPD but not AVPD, and non-BPD controls showed increases in HRV. Their findings for between group differences in emotion regulation difficulties, as measured by DERS subscales, suggest the BPD with co-

occurring AVPD group represented a more severely disordered sub-group of individuals than the group of participants with BPD but not AVPD. It is possible that Gratz et al. (2013) and the present study both captured a moderating effect of BPD severity on HRV, though the two studies captured BPD severity in different ways.

The present finding for a moderating effect of BPD severity on cue reactivity is also consistent with Austin et al.'s (2007) observation that participants with BPD showed decreases in HRV during exposure to emotionally evocative stimuli, while controls showed increases in HRV. Austin and colleagues interpreted their results in terms of Porges' polyvagal theory. They inferred that the BPD group was exhibiting a physiological state of preparedness for defensive behaviors characterized by vagal withdrawal during exposure to emotionally evocative stimuli, (i.e., a fight or flight response). Controls, on the other hand, demonstrated increased vagal activation in response to emotionally evocative stimuli, which the authors posited would support spontaneous social engagement behaviors.

Taken together, these findings suggest individuals with more severe BPD mount a physiological response that goes above and beyond what is called for in the moment. This supports work that suggests individuals with BPD are more sensitive to perceived threat (Dixon-Gordon et al., 2013; Donegan et al., 2003; Lynch et al., 2006), and may help explain why once emotionally dysregulated, people with BPD have difficulty returning to an affective baseline (Glenn & Klonsky, 2009; Selby et al., 2009; Selby & Joiner Jr, 2013). Additionally, these findings may begin to explain the differing results across studies investigating psychophysiological cue reactivity in BPD. Future psychophysiological BPD studies should report, and control for BPD severity. Perhaps most importantly, this finding

highlights the necessity of considering multiple domains of functioning when attempting to understand BPD pathology.

These findings also speak to the discourse on dimensional versus categorical diagnostic systems for BPD. Many have argued that dimensional classification of BPD is more reliable and valid than the current categorical classification systems used in DSM-5 and ICD-10 (e.g., Conway, Hammen, & Brennan, 2012; Trull, Widiger, & Guthrie, 1990). The present findings support the use of a dimensional diagnostic system because they show that there are important autonomic differences in how individuals with varying degrees of BPD severity respond to emotionally evocative stimuli.

Notably, there was a non-significant, large effect size relationship between BPD severity and BPD participants' subjective arousal to the emotionally evocative images. This finding makes it difficult to determine whether the observed physiological responses to the images are indicative of underlying neurological differences in the CAN in individuals with BPD, or a corollary of consciously perceived threat. Future studies will need to disentangle this relationship. A first step toward this end might be to test whether physiological reactivity in individuals with severe BPD changes through the course of treatments such as Dialectical Behavior Therapy to become more similar to healthy controls, or whether it stays the same even as BPD severity ameliorates with treatment.

Hypothesis 3, that during the post-cue exposure recovery period participants with BPD would show continued reductions in parasympathetic tone, and sustained sympathetic activation, while the control group would return to their pre-challenge

physiological baseline, was not supported. Groups appeared to be similar in terms of how they recovered from cue exposure.

The aforementioned a posteriori analyses, however, also highlighted a key consideration in terms of understanding recovery from emotional stimuli in individuals with BPD. It was evident that within the BPD group, BPD severity moderated recovery from exposure to emotionally evocative stimuli, such that participants with greater BPD severity tended to show increases in HRV during cue exposure recovery, while individuals with lower BPD severity tended to show the opposite recovery response, that is, decreases in HRV. It is possible that this reflects natural rebound effects from autonomic perturbation during cue exposure. The large effect sizes for the relationships between BPD severity and parasympathetically mediated HRV from cue exposure to the recovery period, coupled with the small effect size, negative relationship between BPD severity and change in SCV during cue exposure, and during cue exposure recovery, suggests that parasympathetically mediated processes may be more strongly implicated in BPD affective reactivity than sympathetic processes.

Tests for Effects of Substance Use in Participants with Borderline Personality Disorder

The low numbers of participants with BPD endorsing past month, and past year amphetamine, cannabis, cocaine, opiate, and nicotine use, as well as lifetime histories of alcohol and other drug dependence meant planned analysis for these measures could not be carried out. As a result, tests for the effects of substance use in participants with BPD focused on measures for which there was sufficient data to conduct analyses, that is, past month and past year alcohol use.

The hypothesis that frequency of past month and past year alcohol use, as well as quantity of alcohol consumed in a typical week in the past month would be negatively associated with basal levels of target HRV measures in the BPD sample, was not supported. This is perhaps not surprising given the relatively low levels of drinking in the BPD sample, and that moderate alcohol consumption is not known to appreciably affect HRV (Janszky et al., 2005).

The hypothesis that substance use would predict cue exposure response, specifically that greater past month and past year substance use would predict greater autonomic responses to emotionally evocative pictures, was not supported. All analyses for associations between alcohol use and change in physiology from baseline to cue exposure were non-significant. Again, the relatively low levels of alcohol consumption in participants with BPD may account for these null effects.

Hypothesis 4, that greater substance use would predict less autonomic recovery after perturbation was partially supported. Quantity of alcohol consumed in a typical week in the past month was negatively associated with change in SAPD. Slope inspection revealed that greater alcohol use predicted either decreases, or very small increases in SAPD from cue exposure to the recovery period, while those who drank less or not at all were more likely to experience larger increases in SAPD. This finding suggests even at relatively low levels, past month alcohol use may affect dynamic recovery of SAP in response to stressors.

Dissociative Tendencies as a Moderator of Psychophysiological Cue Reactivity

Path modeling was used to test if dissociative tendencies moderate psychophysiological cue reactivity. Dissociative tendencies were found to moderate change in pNN50, and SAPD from baseline to cue exposure. Careful slope inspection indicated that greater trait dissociation was associated with decreases in pNN50 from baseline to cue exposure, while lower levels of trait dissociation predicted increases in pNN50. Further, greater trait dissociation predicted increases or little change in SAPD from baseline to cue exposure, while lower trait dissociation predicted decreases in SAPD.

Previously, Ebner-Priemer et al. (2005) showed that individuals with BPD reporting high levels of state dissociation demonstrated lower orbicularis oculi electromyographic response to acoustic startle compared to individuals reporting low levels of state dissociation, although notably they found no response differences in terms of HR or mean SC. More recently, in a classical conditioning paradigm, Ebner-Priemer et al. (2009) found differences in mean SC response between individuals expressing high versus low levels of state dissociation during exposure to a conditioned stimulus that had been paired with an aversive sound. That is, participants with BPD who had low levels of state dissociation demonstrated significant increases in mean SC in response to the conditioned stimulus during the extinction phase of the study, while participants with high levels of state dissociation showed no change in mean SC.

Although the current investigation assessed the effects of trait and not state dissociation, and utilized emotionally evocative images rather than auditory stressors, the present findings thematically extend Ebner-Priemer and colleagues' previous work by

showing for the first time that greater dissociative tendencies predict lower HRV, and greater BPV in response to an emotionally evocative stressor. It is possible that these results reflect dampening of emotional responding through the ventral vagal complex, a parasympathetic CAN structure that plays a central role in the coordination of sensory perception, affective expression, and cardiac modulation through innervation of the sensory organs, facial and vocalization muscles, and heart (Porges, 2001). So, while the present study showed individuals with BPD reporting low trait dissociation responded to the emotionally evocative stimuli with increased vagal activation in the same way as controls—a response that would support social engagement and behaviors—participants high in dissociative tendencies responded with decreased vagal tone, which would ultimately undermine adaptive responses.

It is noteworthy that this moderation pattern for dissociative tendencies closely reflects the moderation pattern seen in the a posteriori analyses reported above for BPD severity. That is, change in pNN50 from baseline to cue exposure was shown to be negatively associated with BPD severity, just as with dissociative tendencies. This is perhaps not surprising, given dissociation is a diagnostic marker for BPD, and is generally greater in individuals with more severe BPD. Moreover, in the present sample there was a trend toward a positive association between the BPD severity measure (which did *not* contain any direct measures of dissociation) and DES-II scores used to characterize dissociation ($r = .41$, $p = .06$, $d = .90$). Nevertheless, this finding supports the notion that dissociation is a key feature of BPD, such that it is intertwined with BPD pathology at an autonomic level.

Notably, Ebner-Priemer et al. (2005) and the present investigation both found null effects for mean HR, which at face value may suggest that HR is not especially influenced by dissociative tendencies. This conclusion, however, would be premature. It is possible that the stressors used in Ebner-Priemer et al. (2005) and the present investigation were not of sufficient magnitude to elicit a cardiac response from the sympathetic nervous system, or dorsal vagal complex. So, while the stimuli may have been sufficient to engage the ventral vagal complex with its fast acting, myelinated, parasympathetic fibers that predominantly influence HRV, it may not have been sufficient to engage the sympathetic pathway innervating the heart, with its attendant capacity to significantly increase HR. Moreover, the stimuli used in these studies certainly was not of the magnitude necessary to engage the dorsal ventral complex, which is capable of effecting a freeze response, characterized by dramatic drop in HR, and is typically only activated in situations of extreme perceived threat, or hypoxic crisis (Porges, 2001).

Understanding the moderating effect of dissociation on SAPD cue reactivity is more challenging given the present study is the first to investigate the relationship between dissociation and dynamic BP, and little is understood about the role of dynamic blood pressure in emotion regulation. As such, there is little precedent to draw upon. This finding, however, suggests future research on the psychophysiological processes attendant with dissociation will do well to consider indices of BPV.

Limitations

While the present investigation had many methodological strengths including recruiting an ecologically valid sample, matching groups based on sex and age, checking for

effects of medication, time in treatment, and dissociation, and ensuring BPD participants met DSM-IV-TR diagnostic criteria for BPD, some limitations should be noted.

While the majority of BPD participants (14 of 22) were recruited from DBT-RU where they had been comprehensively assessed for Axis I and Axis II disorders, eight BPD participants not recruited from DBT-RU were asked to self-report current and previous psychiatric diagnoses (other than BPD) to reduce participant burden. It is possible that some Axis I and II diagnoses may have been missed in these participants.

In addition, while a priori power analyses (not reported) suggested groups of 18 would be sufficient to find extant group differences on physiological measures, many large effect size results were observed that did not reach statistical significance, suggesting a larger sample size was called for.

Another factor to consider is that while the IAPS images used to evoke an emotional response in the present investigation had been selected by expert consensus, and characterized a range of BPD sensitivities, the image set had not previously been validated with individuals with BPD, and did not evoke an especially powerful subjective response in the present sample.

It should also be noted that while allowing for psychiatric medications within the BPD group reduced the risk of excluding participants with more severe BPD, it may also have affected results in unpredictable ways. It is not clear to what extent differing medication regimes across participants with BPD who were on medication may have affected their physiology at baseline, or in response to and recovery from cue exposure.

Further, it is not clear to what extent medication may have affected individuals' subjective experience of the images.

Similarly, while allowing for comorbidity in the BPD group reduced the likelihood of excluding individuals with more severe BPD, who are more likely to meet criteria for other psychological disorders, this may have also affected results in unpredictable ways. Though the BPD severity measure investigated may have captured some of this variance, and to some extent assuages these concerns, it is not clear to what extent co-occurring disorders may have affected results.

Finally, the rate of substance use in the BPD group was markedly lower than anticipated. This largely precluded planned hypothesis tests concerned with the effects of substance use on ANS processes in individuals with BPD.

Conclusions and Future Directions

The present investigation sought to comprehensively assess psychophysiological differences between individuals with BPD and controls, and examine whether a loss of flexibility in fundamental ANS processes may contribute to the emotion dysregulation observed in BPD. Distinct between group differences were observed at baseline on measures influenced by the sympathetic branch of the ANS, while resting differences in parasympathetic activation were not observed. A priori analyses did not find predicted between group differences, however a posteriori analyses revealed an important moderating effect of BPD severity. The importance of this finding cannot be stressed enough. It speaks to the heterogeneity in BPD pathology observed by clinicians, and suggests that within BPD populations there are fundamental differences in how individuals respond

physiologically to emotionally valenced stimuli, and that this difference is related to BPD severity. This finding also supports the case for moving away from categorical diagnosis of BPD towards dimensional diagnostic systems. Additionally, this finding may begin to explain why individuals with BPD, especially severe BPD, often become dysregulated when confronted with relatively low level stressors, and commonly have great difficulty returning to affective baseline once dysregulated.

Further, no previous study investigating psychophysiological processes in BPD has actively controlled for BPD severity. It is possible that equivocal results in previous studies may have been driven in part by this factor. If this is in fact the case, studying BPD pathology at the level of the mean is inappropriate as it fails to appreciate important inter-individual differences. Future studies should consider and report measures of BPD severity and will benefit from utilizing person-centered, rather than variable-centered analytic strategies (e.g., Bates, Buckman, Eddie, Voelbel, & Freeman, 2013).

Although low levels of substance use in the present BPD sample precluded planned analyses to test for effects of co-occurring substance use on target physiological indices at resting baseline, during cue exposure, and during recovery from cue exposure, recent alcohol use was implicated in changes in SAP variability during recovery from exposure to emotionally evocative images. Future studies using samples of people with BPD and co-occurring, active substance use disorders should attend especially to the effects of alcohol on blood pressure dynamics and the systems that regulate these processes, including the baroreflex.

The picture stimulus set was rated as significantly more arousing by participants with BPD, however, the mean between groups difference was not especially robust. Though the IAPS picture set offers advantages, including being well validated in a variety of clinical, and non-clinical samples, the present findings suggest a more targeted BPD specific image set may be indicated for cue-reactivity studies with people with BPD.

In sum, this investigation supports the postulate that BPD pathology manifests in, or is affected by dysregulation of ANS processes, both at rest, and in response to stimuli. Further, BPD severity appears to be a key factor associated with individuals' responses to emotionally evocative stimuli, and may represent an important, hitherto unrecognized psychophysiological component implicit in BPD heterogeneity.

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Table 1. Participant characteristics by group

	BPD Group Mean/Frequency n = 22	Control Group Mean/Frequency n = 22	t/χ^2	d
Sex (number female)	18	18	0.00	0.00
Age	27.9 (8.1)	27.1 (7.7)	0.33	0.10
Body mass index	24.4 (5.9)	23.0 (4.3)	0.87	0.27
Previous DBT (months lifetime)	3.5 (3.5)	0.0 (0.0)	—	—
Previous therapy (months lifetime)	70.6 (77.4)	2.6 (6.7)	4.10*	1.24

Notes: Standard deviations in parentheses; BPD = Borderline personality disorder, DBT = Dialectical Behavior Therapy; d = Cohen's d effect size estimate; * $p < .05$.

Table 2. Psychological measures by group showing means, standard deviations, and between group differences

	BPD Group Mean n = 22	Control Group Mean n = 22	t/χ^2	d
Acceptance & Action Questionnaire	25.4 (5.7)	29.4 (3.7)	-2.73*	0.91
Beck Depression Inventory	24.0 (10.8)	4.1 (4.0)	8.13*	2.51
BPD Severity (BSL - 23 + DERS)^	143.3 (41.3)	65.6 (16.8)	8.16*	2.52
Borderline Symptom List	40.3 (21.8)	6.8 (8.8)	6.66*	2.53
Difficulties in Emotion Regulation Scale	103.0 (22.1)	58.8 (10.6)	8.46*	3.09
Dissociative Experiences Scale	55.8 (40.5)	15.7 (10.2)	4.51*	1.86
Positive & Negative Affect Schedule				
Positive affect	27.5 (8.2)	27.4 (8.0)	0.04	0.01
Negative affect	19.4 (9.8)	11.4 (3.2)	3.85*	1.52
State/Trait Anxiety Inventory				
State anxiety	38.5 (7.6)	26.9 (5.9)	5.70*	1.76
Trait anxiety	47.1 (6.8)	31.6 (6.3)	7.85*	2.42

Notes: Standard deviations in parentheses; BPD = Borderline personality disorder; d = Cohen's d effect size estimate; * $p < .05$; ^ BPD severity expressed here as raw, combined Borderline Symptom List (BSL - 23) and Difficulties in Emotion Regulation (DERS) scores, however to ensure equal weighting of these measures, BSL - 23 and DERS z -scores were used to calculate BPD severity for all analyses.

Table 3. Alcohol use in the past month and past year, and lifetime alcohol dependence diagnosis, by group, with between group differences

	BPD Group Mean/Frequency <i>n</i> = 22	Control Group Mean/Frequency <i>n</i> = 22	<i>t</i> / χ^2	<i>d</i>
Age initiating drinking [^]	17.1 (3.3)	18.0 (1.8)	-1.15	0.35
Total number of drinking days in a typical week in the past month [^]	1.3 (1.8)	1.8 (2.0)	-0.95	0.29
Total number of drinks in a typical week in the past month [^]	3.3 (5.3)	3.8 (4.1)	-0.35	0.11
Number of drinking days in the heaviest drinking week in the past month [^]	1.95 (2.5)	2.1 (2.0)	-0.20	0.06
Total number of drinks in heaviest drinking week in the past month [^]	5.2 (7.6)	5.8 (5.6)	-0.27	0.08
Number of participants with lifetime diagnosis of alcohol dependence	7	0	8.32*	0.97

Notes: Standard deviations in parentheses; BPD = Borderline personality disorder; *d* = Cohen's *d* effect size estimate; [^]Analyses conducted using participants who reported past year drinking. One BPD participant was in recovery from alcohol dependence and was abstinent from alcohol in the past year, and 3 control participants endorsed trying alcohol, but never becoming drinkers.

Table 4. Drugs other than alcohol use in the past month and past year, and lifetime drug dependence diagnosis, by group, with between group differences

	BPD Group Mean <i>n</i> = 22	Control Group Mean <i>n</i> = 22	<i>t</i> / χ^2	<i>d</i>
<i>Frequency of drug use in past month as number of days</i>				
Amphetamines [‡]	0.00 (0.0)	0.05 (0.2)	—	—
Cannabis	2.95 (7.2)	0.18 (0.5)	1.79	0.78
Cocaine	0.00 (0.0)	0.00 (0.0)	—	—
MDMA	0.00 (0.0)	0.00 (0.0)	—	—
Nicotine [†]	7.41 (12.8)	0.09 (0.3)	2.67*	0.82
Opiates [∞]	0.05 (0.2)	0.00 (0.0)	—	—
<i>Frequency of drug use over the past year as average number of times using per week</i>				
Amphetamines [‡]	0.41 (1.5)	0.00 (0.0)	—	—
Cannabis	1.21 (2.1)	0.36 (1.1)	1.69	0.52
Cocaine	0.14 (0.6)	0.00 (0.0)	—	—
MDMA	0.05 (0.2)	0.00 (0.0)	—	—
Nicotine [†]	21.41 (42.7)	0.36 (1.5)	2.31*	0.71
Opiates [∞]	0.23 (1.1)	0.05 (0.2)	0.78	0.33
Number of participants with lifetime diagnosis of drug dependence [^]	5	0	5.64*	0.77

Notes: Standard deviations in parentheses. *d* = Cohen's *d* effect size estimate; Use frequency includes individuals who report no lifetime use. BPD = Borderline personality disorder; MDMA =

Methylenedioxymethamphetamine; * $p < .05$; * Methamphetamine & prescription amphetamines combined, † Cigarettes, e-cigarettes, and smokeless tobacco combined, ∞ Heroin, methadone, and prescription opioids combined, ^ Reflects dependence to drugs other than alcohol and nicotine.

Table 5. Baseline physiological measures by group showing means, standard deviations, and between group differences

	Baseline			
	BPD	Control	<i>t</i>	<i>d</i>
<i>Heart Rate</i>				
Heart Rate (mean)	74.2 (8.4)	68.2 (9.0)	2.25*	0.70
<i>Heart Rate Variability</i>				
SDNN [†]	49.2 (22.7)	55.4 (27.8)	−0.77	0.24
RMSSD [†]	41.8 (28.2)	48.8 (31.1)	−1.12	0.35
pNN50	17.8 (20.1)	25.7 (19.3)	−1.31	0.41
High Frequency HRV [†]	650.6 (941.1)	858.1 (1431.0)	−0.84	0.26
Low Frequency HRV [†]	844.7 (732.9)	984.3 (1158.0)	−0.34	0.12
Very Low Frequency HRV [†]	646.4 (523.7)	691.6 (698.0)	−0.18	0.06
<i>Blood Pressure</i>				
SAP	123.7 (16.5)	128.1 (15.4)	−0.91	0.28
DAP	64.3 (10.9)	64.8 (10.3)	−0.15	0.05
MAP	83.3 (12.4)	84.4 (11.3)	−0.30	0.09
<i>Blood Pressure Variability</i>				
SAP Deviation	5.5 (2.0)	5.9 (2.4)	−0.59	0.18
DAP Deviation	3.2 (0.9)	3.3 (0.8)	−0.60	0.19
MAP Deviation	3.7 (1.1)	3.8 (1.0)	−0.45	0.14
<i>Skin Conductance Variance</i>				
SC Deviation [†]	0.52 (0.48)	0.21 (0.18)	2.74*	1.02
<i>Respiration</i>				
Respiration Frequency	0.30 (0.06)	0.28 (0.06)	0.98	0.30
Tidal Volume (mean)	350.4 (292.2)	248.1 (136.6)	1.49	0.46

Notes. Standard deviations in parentheses; d = Cohen's d effect size estimate; SDNN = Standard deviation of all normal-to-normal intervals, RMSSD = Root of the mean squared differences of successive normal-to-normal intervals, pNN50 = percent of normal-to-normal adjacent intervals greater than 50ms, HRV = Heart rate variability, SAP = Systolic arterial pressure, DAP = Diastolic arterial pressure, MAP = Mean arterial pressure, SC = Skin conductance; * $p < .05$;

[†] Logarithmically transformed data used for t-tests. BPD group $n = 21$ (after one influential outlier was excluded), control group $n = 22$.

Table 6. Average scores with standard deviations for physiological indices by group at baseline, during cure exposure, and during the recovery period, as well as results from mixed models testing for main effects of group, time, and their interaction on measures of physiology

	Baseline	Cue Exposure	Recovery Period	Main Effect Group <i>F</i>	Main Effect Time <i>F</i>	Group x Time Interaction <i>F</i>
<i>Heart Rate (mean)</i>				4.72*	5.01*	1.72
BPD	74.2 (8.4) [§]	74.6 (8.5)	74.9 (8.2)			
Control	68.2 (9.0)	70.0 (8.2)	68.8 (9.1)			
<i>SDNN</i>				0.22	4.37*	0.77
BPD	49.2 (22.7)	50.7 (19.9)	55.2 (21.0)			
Control	55.4 (27.8)	55.5 (31.2)	56.4 (26.2)			
<i>High Frequency HRV</i>				0.15	0.38	1.12
BPD	650.6 (941.1)	696.7 (819.9)	718.9 (736.4)			
Control	858.1 (1431.0)	945.1 (2021.8)	944.0 (1747.3)			
<i>Low Frequency HRV</i>				0.00	1.12	1.00
BPD	844.7 (732.9)	925.5 (911.3)	1030.8 (992.7)			
Control	984.3 (1158.0)	1096.6 (1332.0)	893.7 (837.8)			
<i>SAP Variability</i>				0.02	1.64	2.06
BPD	5.5 (2.0)	5.5 (2.7)	6.3 (2.7)			
Control	5.9 (2.4)	5.5 (2.2)	6.0 (3.1)			
<i>SC Variance</i>				7.05*	4.43*	0.05
BPD	0.52 (0.48) [§]	0.75 (0.90)	0.62 (0.84)			
Control	0.21 (0.18)	0.34 (0.35)	0.22 (0.34)			

Notes. Standard deviations in parentheses; BPD = Borderline personality disorder, SDNN = Standard deviation of all normal-to-normal intervals, HRV = Heart rate variability, SAP = Systolic arterial pressure, SC = Skin conductance; * $p < .05$; [§] denotes significant difference in physiology between groups at baseline, $p < .05$; Main effect group $df = 1, 42$, Main effect time $df = 2, 42$, Interaction term $df = 2, 42$.

Table 7. Combined groups' physiological means and standard deviations by task, showing results for least square means post hoc tests

	Baseline n = 43	Cue Exposure n = 44	Recovery Period n = 43
Heart Rate (mean)	71.1 (9.1)	72.3 (8.6)*	71.9 (9.1)
SDNN	52.4 (25.3)	53.1 (26.0)	55.8 (23.9) ^f
High Frequency HRV	756.8 (1206.9)	820.9 (1529.9)	828.9 (1318.3)
Low Frequency HRV	916.1 (965.0)	1011.1 (1131.2)	963.8 (912.0)
SAP Variability	5.7 (2.2)	5.5 (2.5)	5.9 (2.5)
SC Variance	0.37 (0.4)	0.55 (0.7)*	0.43 (0.7) [‡]

Notes. Standard deviations in parentheses; SDNN = Standard deviation of all normal-to-normal intervals, HRV = Heart rate variability, SAP = Systolic arterial pressure, SC = Skin conductance; * Denotes significant change from baseline to cue exposure, $p < .05$; [‡] Denotes significant change from cue exposure to recovery period, $p < .05$; ^f Denotes significant change from baseline to recovery period, $p < .05$.

Table 8. Relationships between borderline personality disorder severity and change in physiology from baseline to cue exposure, as well as from cue exposure to recovery period, in participants with borderline personality disorder

	Change from Baseline – Cue Exposure		Change from Cue Exposure – Recovery Period	
	<i>r</i>	<i>d</i>	<i>r</i>	<i>d</i>
Heart Rate (mean)	.38	0.81	–.13	0.27
SDNN [†]	–.34	0.72	.27	0.56
RMSSD [†]	–.29	0.60	.44*	0.98
pNN50	–.61*	1.54	.60*	1.48
High Frequency HRV [†]	–.36	0.78	.45*	1.01
Low Frequency HRV [†]	–.33	0.70	–.03	0.06
SAP Deviation	.12	0.25	.14	0.28
SC Variance [†]	–.26	0.53	–.10	0.21

Notes. *d* = Cohen's *d* effect size estimate; SDNN = Standard deviation of all normal-to-normal intervals, RMSSD = Root of the mean squared differences of successive normal-to-normal intervals, pNN50 = Percent of normal-to-normal adjacent intervals greater than 50ms, HRV = Heart rate variability, SAP = Systolic arterial pressure, SC = Skin conductance; * $p < .05$;

[†] Logarithmically transformed data used for general linear model; $N = 22$.

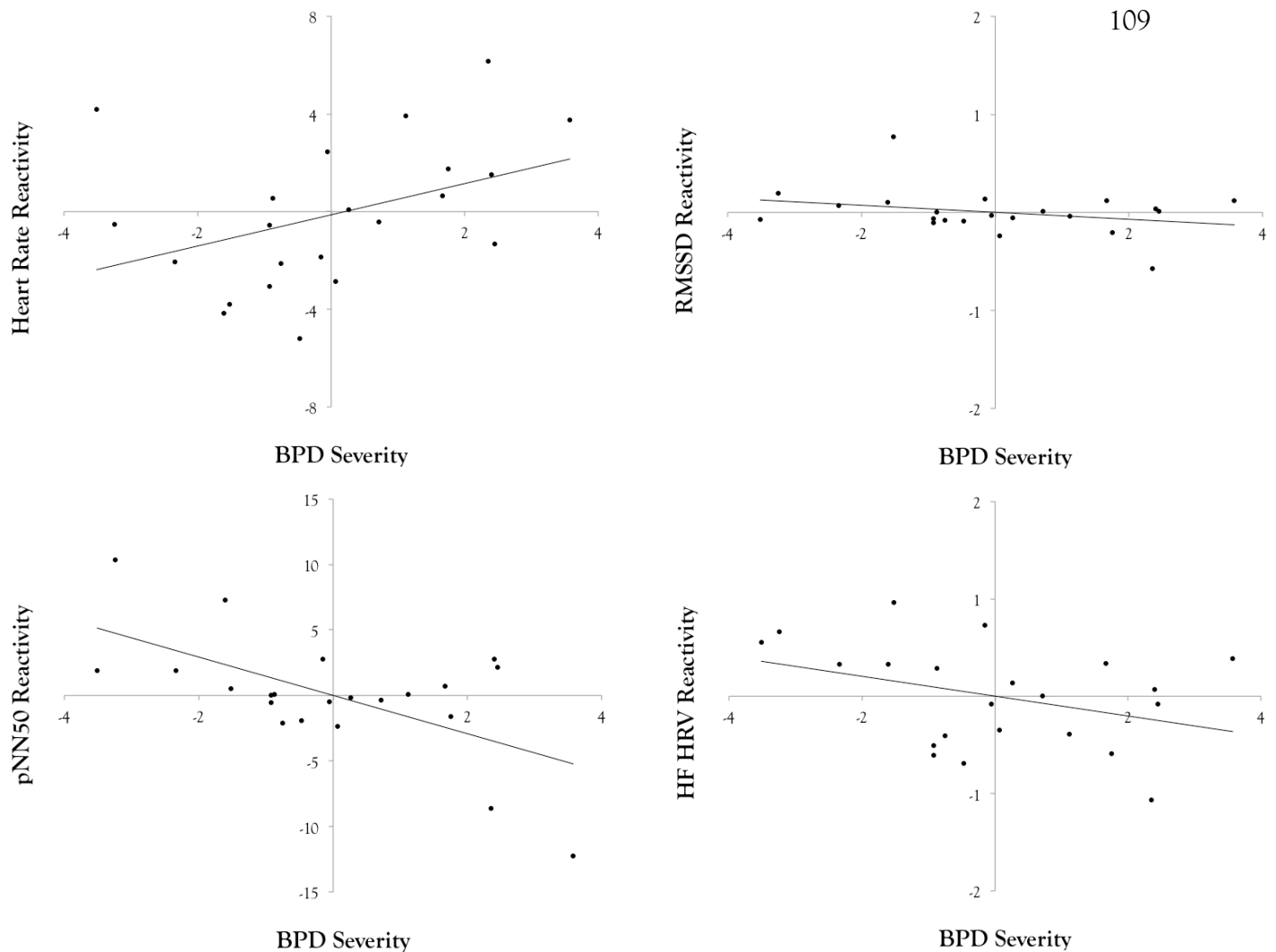


Figure 1. Associations between borderline personality disorder (BPD) severity and heart rate, root of the mean squared differences of successive normal-to-normal intervals (RMSSD), percent of normal-to-normal adjacent intervals greater than 50ms (pNN50), as well as high frequency heart rate variability (HF HRV) during exposure to emotionally evocative images. BPD severity is expressed as z-scores (standardized units); positive values reflect greater BPD severity while negative values reflect lesser BPD severity. Physiological measures are expressed as residuals (i.e., change scores derived from regressing cue exposure physiology values onto their respective physiology value during baseline). Positive values for physiological measures reflect increases in that measure from baseline to cue exposure, while negative values reflect decreases in that measure from baseline to cue exposure.

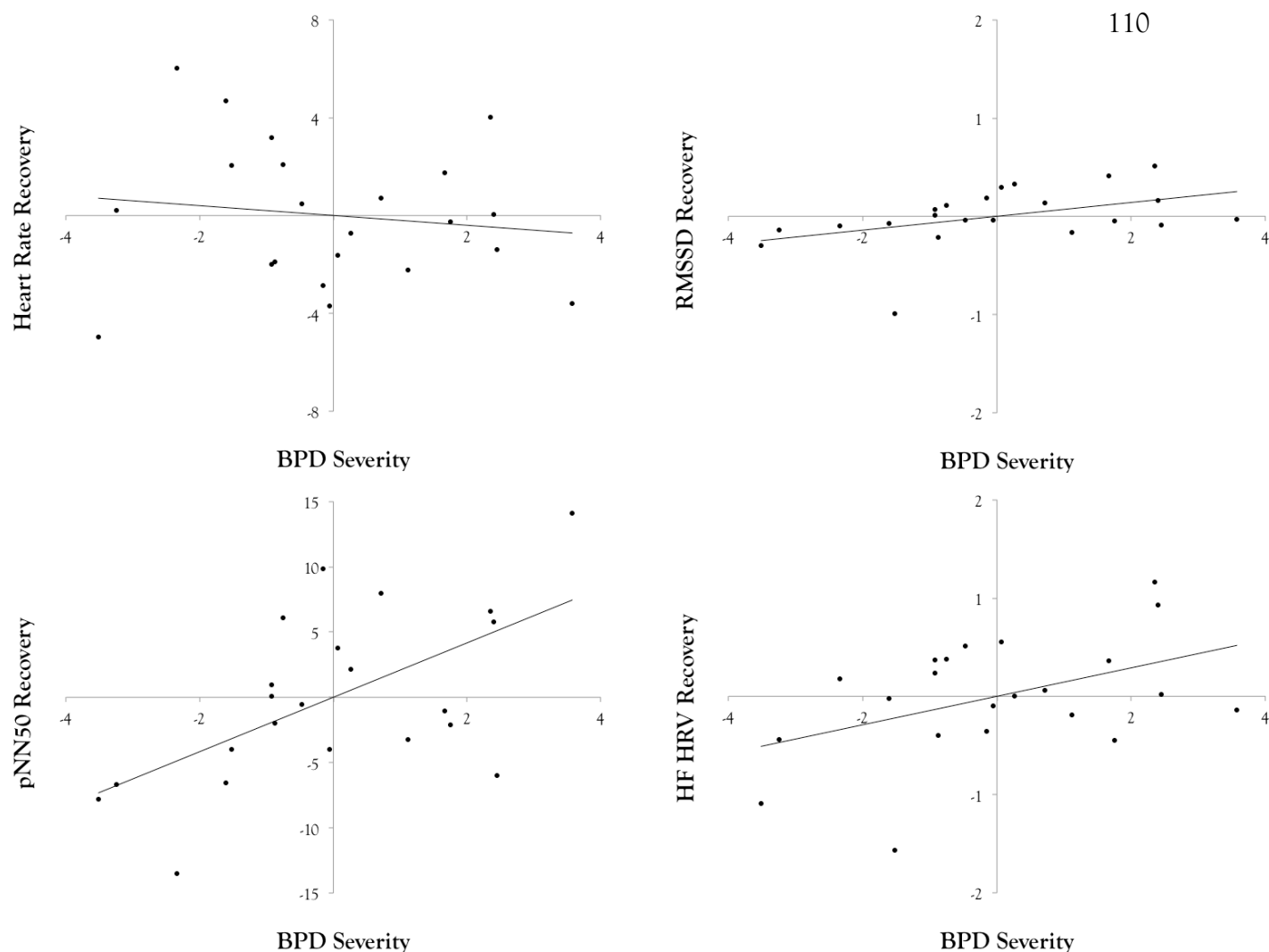


Figure 2. Associations between borderline personality disorder (BPD) severity and heart rate (HR), root of the mean squared differences of successive normal-to-normal intervals (RMSSD), percent of normal-to-normal adjacent intervals greater than 50ms (pNN50), as well as high frequency heart rate variability (HF HRV) during recovery from exposure to emotionally evocative images. BPD severity is expressed as z-scores (standardized units); positive values reflect greater BPD severity while negative values reflect lesser BPD severity. Physiological measures are expressed as residuals (i.e., change scores derived from regressing recovery period physiology values onto their respective physiology value during cue exposure). Positive values for physiological measures reflect increases in that measure from cue exposure to the recovery period, while negative values reflect decreases in that measure from cue exposure to the recovery period.

Appendix A.

International Affective Picture System (IAPS) images by image number (Sloan et al., 2010).

	IAPS Picture Number
1.	2025
2.	2053
3.	2100
4.	2110
5.	2120
6.	2130
7.	2141
8.	2250
9.	2271
10.	2272
11.	2276
12.	2399
13.	2410
14.	2441
15.	2595
16.	2702
17.	2710
18.	2715
19.	2745
20.	2752
21.	2800
22.	2810
23.	2900
24.	3022
25.	4621
26.	4635
27.	4650
28.	4660
29.	6311
30.	6313
31.	6315
32.	6350
33.	6360
34.	6561
35.	9041
36.	9405