



Heart rate variability as a potential indicator of positive valence system disturbance: A proof of concept investigation[☆]



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ABSTRACT

One promising avenue toward a better understanding of the pathophysiology of positive emotional disturbances is to examine high-frequency heart rate variability (HRV-HF), which has been implicated as a potential physiological index of disturbances in positive emotional functioning. To date, only a few psychopathology relevant studies have systematically quantified HRV-HF profiles using more ecologically valid methods in everyday life. Using an experience-sampling approach, the present study examined both mean levels and intra-individual variability of HRV-HF – as well as comparison measures of cardiovascular arousal, sympathetic activity, and gross somatic movement – in everyday life, using ambulatory psychophysiological measurement across a six-day consecutive period among a spectrum of community adult participants with varying degrees of positive valence system disturbance, including adults with bipolar I disorder (BD; $n = 21$), major depressive disorder (MDD; $n = 17$), and healthy non-psychiatric controls (CTL; $n = 28$). Groups did not differ in mean HRV-HF, but greater HRV-HF instability (i.e., intra-individual variation in HRV-HF) was found in the BD compared to both MDD and CTL groups. Subsequent analyses suggested that group differences in HRV-HF variability were largely accounted for by variations in clinician-rated manic symptoms. However, no association was found between HRV-HF variability and dimensional measures of positive affectivity. This work provides evidence consistent with a quadratic relationship between HRV-HF and positive emotional disturbance and represents a valuable step toward developing a more ecologically valid model of positive valence system disturbances and their underlying psychophysiological mechanisms within an RDoC framework.

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Patterns of activation in the autonomic nervous system are essential to emotional responding and well-being (e.g., Levenson et al., 1992). Of particular importance is cardiac vagal tone, a measure of parasympathetic activity in the autonomic nervous system that has been associated with emotional functioning and well-being (e.g., Porges, 1995; El-Sheikh et al., 2001; Oveis et al., 2009; Kok & Fredrickson, 2010). One promising avenue toward a better understanding of the pathophysiology of positive emotion disturbances is to examine HRV, a measurement of activity in the parasympathetic nervous system, which has been implicated as a potential physiological index of disturbances in both positive emotional functioning and emotion regulation in healthy and clinical populations (e.g., Gruber, 2011; Kogan et al., 2014; Oveis et al., 2009). Along this line, some work has been done to quantify high frequency HRV profiles

using more ecologically valid methods in everyday life (e.g., Pfaltz et al., 2015; Rosenthal et al., 2015; Seeley et al., 2015). Building on this body of work, the present investigation employed a daily experience-sampling approach across a six-day consecutive interval to examine both mean levels and intra-individual variability of high-frequency HRV, along with relevant comparison channels for purposes of evaluating specificity, in community adult participants with and without clinical histories of mood symptomatology who differed in dispositional positive affectivity. Our focus on variations along a continuum of positive affectivity is consistent with the dimensional-systems approach of the Research Domain Criteria (RDoC) initiative (e.g., Cuthbert & Kozak, 2013; Cuthbert & Insel, 2013; Insel et al., 2010; Sanislow et al., 2010).

1. Heart rate variability and emotional functioning

High-frequency HRV (or HRV-HF) reflects the influence of the tenth cranial nerve (i.e., the vagus nerve) on the cardiovascular system. The vagal pathway influences emotional experience, regulation, and communication (e.g., Porges, 1995, 2007; Thayer & Lane, 2000). Importantly,

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the vagal pathway also serves to regulate cardiovascular arousal and acts as a “brake” to the sympathetic nervous system, and is important to the regulation of emotional experience in that it can be flexibly engaged (vagal activation) to decrease sympathetic system activation, or can be disengaged (vagal withdrawal) to allow for greater sympathetic system activation. In this sense the vagal brake acts to regulate autonomic nervous system activity in response to changing environmental demands.

Empirical research confirms the central role of HRV-HF in emotion functioning, particularly positive emotional functioning. For example, in adults greater HRV-HF has been associated with increased self-reported positive emotionality (Oveis et al., 2009), goal directed behavior (Geisler & Kubiak, 2009), and also greater life satisfaction and well-being (Geisler et al., 2010; Kok & Fredrickson, 2010). By contrast, decreased HRV-HF has been linked to poorer psychological outcomes including greater self-reported trait anxiety (e.g., Thayer et al., 1996), self-reported hostility (e.g., Sloan et al., 1994), and clinical depression (e.g., Rottenberg, 2007). Taken together, these studies suggest that HRV-HF functioning may be closely related to positive affectivity, the dispositional dimension that relates most to the positive valence system (PVS) domain of the RDoC framework. Thus, HRV-HF appears to be a psychophysiological measure of importance to an understanding of PVS disturbances. We note, however, an elegant and alternative (though not incompatible) perspective that HRV may also reflect variations in emotion regulatory capacity that have been demonstrated in relation to both internalizing and externalizing psychopathology (e.g., Beauchaine, 2001; Beauchaine, 2012; Beauchaine & Gatzke-Kopp, 2012). This well-studied perspective on HRV by Beauchaine and colleagues suggests that HRV may indeed serve a broader role as an indicator of affective-regulatory dysfunction more generally in other psychopathologies. For the purposes of the present investigation, and given our specific focus on HRV as it relates to BD and MDD, we take a more narrow slice of the affective regulatory perspective on HRV-HF by focusing on its potential role as an indicator of PVS disturbances.

An entry point for beginning to investigate the role of HRV-HF in emotional functioning is to examine variation in participant samples characterized by disturbances in positive emotional functioning, including individuals from the community with mood disorders such as BD and MDD. Available evidence suggests that disorders of these types entail PVS disturbances associated with abnormalities in HRV. While this body of research focuses on traditional DSM-IV disorder categories, we view it as an important empirical foundation for moving toward an RDoC-dimensional analysis of affective-physiological processes relevant to health outcomes. In the case of BD, individuals suffering from this condition experience intense positive affect that is difficult to regulate and is associated with severe functional impairment, morbidity, and even mortality (e.g., Dilsaver, 2011). Indeed, a cardinal symptom of BD is difficulty in controlling intense positive emotions (e.g., Gruber, 2011; Johnson et al., 2007). For example, both BD patients and young adults at risk for developing BD report sustained elevations in positive emotion following a happy mood induction compared to a healthy control group (Farmer et al., 2006) and continue to experience positive emotion across negative and even neutral contexts (Gruber et al., 2008, 2011b). Furthermore, compared to healthy controls, BD patients exhibit a tendency to passively dwell on, rather than actively exert control over, positive feelings (Gruber et al., 2011a; Johnson et al., 2008). Despite the potential relevance of HRV-HF to BD, little research has examined HRV functioning in BD. In one study, higher mean HRV-HF was associated with risk for BD as indexed by high scores on a scale measure of hypomanic tendencies (Gruber et al., 2008; though also see Henry et al., 2010). On the other hand, individuals at risk for BD, and diagnosed with BD, exhibit greater HRV-HF in the context of emotional film viewing (Gruber et al., 2008, 2011a, 2011b, 2011c). However, to date no study has examined HRV-HF in more naturalistic, everyday contexts, or evaluated whether fluctuations in HRV-HF (as distinguished from mean levels) may operate as an indicator of PVS disturbance.

Although available evidence points clearly toward deficits in negative emotion experience and regulation in MDD (e.g., Kasch et al., 2002; Nolen-Hoeksema, 1991), less is known about positive emotion regulation among MDD patients. This is important as current models of MDD specify core deficits in positive emotion that differentiate this condition from other forms of psychopathology, including anxiety disorders (e.g., Kring & Bachorowski, 1999; Watson et al., 1988). Specifically, MDD patients tend to experience difficulty in generating, maintaining, and enhancing positive emotions over time (Garber, Braafladt, & Weiss, 1995; McMakin et al., 2009) and report less happiness to positive film stimuli compared to a healthy control group (Rottenberg et al., 2002a, 2002b). Depressed individuals also exhibit impaired ability to enhance and sustain positive emotion through the process of savoring (e.g., Sloan et al., 1994).

Most studies to date that have examined HRV-HF in MDD have been completed in laboratory settings where individuals respond to presented stimuli. Studies of this kind have produced mixed results (Rottenberg et al., 2002b). Some work has demonstrated lower levels of HRV in individuals with MDD (e.g., Rechlin et al., 1994), and found lower mean HRV-HF levels to be associated with more persistent depressive symptom course (Chambers & Allen, 2002; Rottenberg et al., 2002a, 2002b). Fewer research studies have examined HRV-HF variability in individuals with MDD. One study by Rottenberg (2007) showed that individuals with MDD exhibited less HRV-HF variability compared to healthy adults.

Importantly, the literature on vagal activity and its association with PVS-related measures has also produced apparently contradictory findings. On the one hand, high levels of vagal activity have been associated with resilience and adaptive levels of positive emotion and well-being (e.g., Geisler & Kubiak, 2009; Kok & Fredrickson, 2010; Oveis et al., 2009). On the other hand, extremely high levels of vagal activity are also associated with clinical measures of mania risk and bipolar disorder diagnosis (Gruber et al., 2008, 2011b), suggesting that greater vagal activity may not always be better for social functioning. This literature suggests that HRV-HF measurement does not bear a simple linear relationship with positive emotional functioning. Rather, consistent with a recent quadratic vagal activity hypothesis (Kogan et al., 2014), the degree of vagal activity (as measured via HRV-HF) is best understood as an adaptive response that promotes healthy positive emotional outcomes up to a point but that at very high or low levels it can become clinically maladaptive. Based on this hypothesis, we predicted that clinical conditions characterized by PVS disturbances – including both low levels of positive emotionality (i.e., depression) and high levels of positive emotionality (i.e., bipolar disorder) – would demonstrate associated core disruptions in HRV-HF functioning.

2. Variability in HRV-HF as an important but understudied target

Although important, a complete understanding of PVS requires more than an understanding of overall levels of positive emotion but also how that process varies, or fluctuates, dynamically over time (Gruber et al., 2013a; Davidson, 1998, 2015). Prior work has demonstrated that variability in positive emotional processes, frequently operationalized as the within-person standard deviation of emotions over time (e.g., Eaton & Funder, 2001), can be reliably measured and is independent of overall emotion levels (Chow et al., 2005; Trull et al., 2008). Measurement of variability in PVS-relevant psychophysiological variables, such as HRV-HF, provides an alternative to report-based assessments of positive emotion.

The idea that measurement of HRV-HF across time points can provide information of clinical importance is supported by research suggesting that greater variability in psychologically-relevant systems reflects instability of the given system and leads to greater vulnerability and distress on the system. This is consistent with broader mechanistic accounts of emotional variability, which suggest that greater self-reported emotional variability signals psychological instability associated with distress and mental illness (Gruber et al., 2013a, 2013b; Kashdan & Rottenberg,

2010; Waugh et al., 2011). Consistent with this notion, greater variability in self-reported negative emotion is associated with increased depressive symptoms (Peeters et al., 2006), borderline personality disorder (Trull et al., 2008), and neuroticism (Eid & Diener, 1999), and greater variability in self-reported positive emotion is associated with increased depressive symptoms and decreased functioning (e.g., Gruber et al., 2013a, 2013b). While much of this research has examined self-reported PVS variability, some work suggests that greater variability in psychophysiological relevant systems (such as HRV-HF) should also relate to worse psychological health (e.g., categorical and dimensional measurements of mood symptoms). This work underscores the importance of understanding HRV-HF variability as a psychophysiological indicator of positive emotional functioning.

Three initial studies provide support for the value of variation in HRV-HF as an index of PVS-related processes. First, Rottenberg (2007) found that HRV-HF withdrawal while watching a negative film clip was associated with recovery of depression symptoms, and HRV-HF activation during the negative film clip was associated with maintenance of depression symptoms. Thus, in response to certain negative stimuli, it may be more beneficial to exhibit HRV-HF withdrawal rather than HRV-HF activation. Second, greater HRV-HF activation in response to positive stimuli has been linked to increased positive emotionality and social connectedness (e.g., Kok & Fredrickson, 2010). Finally, a recent study by Muhtadie et al. (in press) showed that individuals high in vagal flexibility – operationalized as higher cardiac vagal tone at rest during cognitive demand – exhibited greater social-emotional perception and heightened social sensitivity. Thus, the ability to flexibly engage or disengage HRV-HF depending on context may be a crucial component of adaptive emotional functioning. However, additional studies that assess intra-individual HRV-HF variation across contexts in clinically relevant populations are needed to clarify how HRV-HF variability relates to PVS functioning.

3. The present investigation

The present investigation examined differing parameters of HRV (i.e., HRV-HF mean levels or HRV-HF_{mean}, along with HRV-HF stability or HRV-HF_{SD}) in relation to both categorical DSM-IV diagnosis (i.e., BD, MDD, and CTL) and a more RDoC-oriented dimensional measure of positive affectivity (i.e., trait positive affectivity) using an ecologically valid and rigorous experience-sampling method (ESM) approach to characterize naturalistically occurring psychophysiological measurements. Along with HRV-HF (mean and standard deviation), we collected comparison measures of general cardiovascular arousal (i.e., heart rate or HR), sympathetic nervous system activity (i.e., skin temperature or SKT), and gross somatic movement (or GSM) to evaluate the specificity of predicted relationships for HRV-HF. This approach enabled us to examine HRV-HF_{SD} naturalistically, and a focus on community adults enabled us to examine emotional disturbance and regulation independent of the more phasic influences of mood symptoms, and represents a first step toward understanding which aspects of physiology may reflect trait indicators versus mood-state specific characteristics. By examining PVS disturbances as indexed by HRV-HF across differing clinical groups (consistent with RDoC recommendations) and in relation to dimensionally measured positive affectivity, we sought to gain insights into normative emotional processes and dysfunction in such processes as relevant to clinical health outcomes. While the current work focused on clinical samples with validated diagnoses as opposed to dimensional measurement in its sampling strategy, the dimensional measures of positive affectivity were collected from the groups under investigation in the form of quantitative scales assessing state and trait positive affectivity. This work, in light of previous research, was undertaken with the following specific aims:

Aim 1: Test for group differences in HRV-HF. The study used a between-groups design, so the first aim was to characterize the previously recruited DSM-IV groups (i.e., BD, MDD, and healthy control) in terms of psychophysiological variables relevant to the RDoC PVS

domain – i.e., differing parameters of HRV-HF. More specifically, we tested two competing hypotheses regarding potential group differences in HRV-HF_{SD}. One perspective, which we refer to as the *HRV-HF instability hypothesis*, posits that greater HRV-HF_{SD} scores should be associated with positive emotional disturbance. This hypothesis is based on previous work showing that BD spectrum disorders are associated with greater self-reported positive emotion variability (Lovejoy & Steuerwald, 1995), and that greater self-reported emotion variability is related to greater number of depressive symptoms in BD (Bonsall et al., 2012) and non-clinical populations (Gruber et al., 2013a, 2013b). As applied to this study, this perspective predicts that the more severe emotional variability of BD will appear as *increased* HRV-HF_{SD} in BD versus MDD and CTL groups. The second competing hypothesis is that restricted HRV-HF_{SD} should lead to impaired emotional functioning. This hypothesis is based on the polyvagal theory, which suggests that rigid HRV-HF functioning reflects a malfunctioning or “stuck” vagal brake (Porges, 1995, 2007) and lowered vagal sensitivity (e.g., Muhtadie et al., in press). Moreover, rigid and context-insensitive emotional responding has been found in BD as evidenced by reduced HRV-HF in response to emotional film clips (Gruber et al., 2011a, 2011b, 2011c) and when attempting to down-regulate from a positive mood induction (Gruber, 2011). As applied to the current study, this perspective predicts that the more severe emotional variability of BD will appear as *decreased* HRV-HF_{SD} in BD versus MDD and CTL groups.

As a supplement to the groups analyses, and a link to Aim 2 (below), we also examined HRV in relation to specific symptoms of mania that characterize BD. We predicted that higher manic symptoms would be associated with increased HRV-HF_{SD}.

Aim 2: Dimensional measures of positive affectivity and HRV-HF. The second aim was to connect findings for BD (Aim 1) to the RDoC PVS conception by examining HRV in relation to continuous variations in self-reported positive affectivity across study participants. Paralleling our prediction for manic symptoms, we predicted that higher positive affectivity would be related to HRV-HF instability as evidenced by increased HRV-HF_{SD}.

4. Method

4.1. Participants

Participants between the ages of 18–60 were recruited via flyers posted around the community or an online advertisement (e.g., www.craigslist.org) from the greater New Haven, Connecticut, USA region. Participants responded to one of three separate study advertisements: a study on “emotion and mood” for healthy controls, on “bipolar disorder and emotion” for the BD group, and on “history of depression and emotion” for the MDD group. Interested participants completed a brief phone screen with a trained researcher, and were invited to the laboratory for a diagnostic evaluation to determine final study eligibility. Of the 120 participants invited for a diagnostic evaluation, 111 were eligible for the broader study protocol, and 84 were included in ESM study analyses. Of these 66 had usable psychophysiological data (i.e., consented to participate in the psychophysiological portion and had usable data for the full study duration) and were included in the final analyses.

Specifically, 21 were participants diagnosed with BD type I in remission, the healthy control (CTL) group comprised 28 participants not meeting current or past criteria for any DSM-IV-TR Axis I disorder (First, Spitzer, Gibbon, & Williams, 2007) and the MDD clinical comparison group comprised 17 participants with MDD in remission. Both BD and MDD groups were currently remitted (i.e., not in a current manic, depressed, or mixed mood phase) in order to examine more trait-like

patterns of emotion control independent of current mood episode. Exclusion criteria for all groups included reports of a history of severe head trauma, stroke, neurological disease, severe medical illness (e.g., autoimmune disorder, cardiovascular disease, HIV/AIDS), or current alcohol or substance abuse in the past six months. See Table 1 for demographic and clinical characteristics.

4.2. Measures of clinical functioning

4.2.1. Diagnostic evaluation

Diagnoses of BD, MDD, and CTL status were confirmed using the Structured Clinical Interview for DSM-IV (SCID-IV; First, Spitzer, Gibbon, & Williams, 2007). Trained clinical psychology faculty, psychology doctoral candidates, or post-baccalaureate research fellows administered the SCID-IV.

4.2.2. Mood symptoms

The current symptoms of mania were measured using the Bech-Rafaelsen Mania Scale (BRMS; Bech et al., 1979). The current symptoms of depression were measured using the Inventory of Depressive Symptomatology (IDS-C; Trivedi et al., 2004). The BRMS is an 11-item, clinician-rated measure of current manic symptoms with scores ranging from 0 to 44, and the IDS-C is a 30-item, clinician-rated measure of current depressive symptoms with scores ranging from 0 to 84. Current remitted mood status (i.e., neither manic, depressed, nor mixed mood state) for all groups was verified according to both current SCID-IV criteria and cutoff scores on the BRMS (≤ 15), and IDS-C (≤ 11).

4.2.3. Global functioning

The Global Assessment of Functioning (GAF; DSM-IV Axis V) Scale was used to assess general functioning in the past week. The GAF assesses overall psychological, social, and occupational functioning on a scale from 1 (lowest level of functioning) to 100 (highest level of functioning).

4.3. State and trait positive affectivity

4.3.1. State positive affectivity

Self-reported state positive affectivity (PA) was assessed using a version of the modified Differential Emotions Scale (mDES; Cohn et al., 2009), consisting of 10 individual positive emotions (i.e., amusement, awe, compassion, contentment, gratitude, hope, interest, joy, love, pride) rated on a 1 (not at all) to 5 (extremely) with a time frame of 'How much do you feel each emotion right now'. From these, a mean PA score was created for each separate experience-sampling event and averaged across all experience-sampling events.

4.3.2. Trait positive affectivity

Self-reported trait positive affectivity (PA) was assessed using a modified trait version of the mDES completed at the end of the diagnostic interview consisting of 10 individual positive emotions (i.e., amusement, awe, compassion, contentment, gratitude, hope, interest, joy, love, pride) rated on a 1 (not at all) to 5 (extremely) with a time frame of 'How much do you feel each emotion on the average, or in general', from which a mean trait PA score was created.

4.4. Psychophysiological data

The Zephyr™ BioHarness™ device (Zephyr Technology, Auckland, New Zealand) is a wireless physiological monitoring system used to collect ambulatory psychophysiological data (e.g., Hailstone & Kilding, 2011). Physiological data were continuously measured at 250 Hz during the entire study period, and a timestamp on the physiological data enabled the synchronization of physiological data with the onset of the different sampling event periods. Data were analyzed offline using a combination of AcqKnowledge v3.9 (Biopac Systems, Inc, Gahanna,

OH) and MindWare software (MindWare Technologies, Inc., Gahanna, OH) described below. Artifacts and recording errors were corrected offline and values more or less than 3.0 standard deviations were deemed outliers and Winsorized (reassigned a value at the next highest or lowest value that was not an outlier). All values reflect means and standard deviation scores obtained collected four times each day in 40 minute bins (to ensure sufficient HRV-HF sampling intervals) centered around each of the 24 distinct sampling periods (i.e., four times each day for six consecutive days) when self-report ratings were obtained (cf. Gruber et al., 2013a, 2013b). Specifically, each bin was comprised of several smaller 5-minute bins which were subsequently averaged and aggregated into the larger 40-minute bin.

The primary measure of focus was HRV-HF as a psychophysiological indicator of parasympathetic nervous system activity. However, we also report findings for four other comparison measures of peripheral autonomic activity – general cardiac activity (heart rate [HR] and respiratory frequency [RESP]), sympathetic nervous system activity (skin temperature [SKT]), and gross somatic movement (GSM) – to rule out motion-related confounds (given the ambulatory nature of assessments for the study). To further ensure the specificity of our hypothesized results with respect to variability in HRV-HF, mean levels of HRV-HF were also controlled where appropriate (see below). For both our primary variables of interest, parameters of HRV-HF (i.e., HRV-HF_{mean} and HRV-HF_{SD}), and the four comparison measures, we computed scores consisting of the mean (i.e., average across the 24 distinct sampling periods or bins) and intra-individual standard deviation (i.e., within-person standard deviation across the same sampling periods).

4.4.1. High frequency heart rate variability (HRV-HF)

HRV-HF was employed as the primary psychophysiological measure of interest. HRV-HF is a noninvasive index of parasympathetic nervous activity. HRV-HF has been associated with positive emotion functioning (e.g., Kok & Fredrickson, 2010; Porges, 1995; Oveis et al., 2009), and emotion regulation capacity (Butler et al., 2006) in general and in BD specifically (Gruber, 2011; Gruber et al., 2011b). HRV-HF refers to the natural variation in heart rate due to respiratory factors (Berntson et al., 1997; Grossman & Taylor, 2007). During inspiration, the heart period (distance between R-spikes) becomes smaller; during expiration,

Table 1
Demographic and clinical characteristics.

	BD (n = 28)	MDD (n = 17)	CTL (n = 21)	Statistic
<i>Demographic</i>				
Age (yrs)	31.63 (10.02)	32.19 (12.22)	30.48 (8.09)	F = 0.150
Female (%)	58.8%	70.6%	66.7%	$\chi^2 = 0.24$
Education (yrs)	15.28 (2.31)	15.12 (2.50)	16.10	F = 0.97
Employed (%)	43.8%	35.3%	69.2%	$\chi^2 = 17.42$
Partnered (%)	37.5%	17.6%	26.9%	$\chi^2 = 7.84$
<i>Clinical</i>				
BRMS	2.29 (2.19)	1.59 (1.54)	1.04 (1.04)	F = 3.62 ^a
IDS-C	5.00 (4.15)	5.29 (2.69)	1.75 (1.86)	F = 6.24 ^{a,c}
GAF	75.72 (7.36)	79.82 (6.67)	88.25 (3.03)	F = 31.69 ^{a,b,c}
Age at onset (yrs)	15.40 (7.91)	15.47 (7.33)	–	F = 0.001
Illness duration (yrs)	13.15 (12.23)	23.37 (14.87)	–	F = 2.56
# comorbid disorders	0.71 (1.19)	0.59 (0.94)	–	F = 5.29 ^b
# depressive episodes	11.13 (15.95)	4.15 (2.29)	–	F = 2.07
# manic episodes	9.57 (14.96)	–	–	–

Note: BD = bipolar I disorder group; MDD = major depressive disorder group; CTL = healthy control group; Employed = employed full-time or part-time; partnered = married or live-in-partner; YMRS = Young Mania Rating Scale; IDS-C = Inventory to Diagnose Depression; GAF = Global Assessment of Functioning; SILS = Shipley Institute of Living Scale; age at onset = age of first depressive or manic episode; # comorbid disorders = the number of current DSM-IV-TR Axis I comorbidities; Mean values are displayed with standard deviations in parentheses where applicable.

^a p < 0.05 for BD and CTL.
^b p < 0.05 for BD and MDD.
^c p < 0.05 for MDD and CTL.

the heart period increases. Specifically, the ECG signal was digitized (250 Hz) and IBI series was derived, and artifacts were identified and edited (Berntson et al., 1990, 1997) using AcqKnowledge v3.9 software. These individual R–R intervals were then exported into Mindware HRV v.3.0 software for analysis (Mindware Technologies, Inc., Gahanna, OH). Using a power spectrum approach, HRV-HF was quantified as the integral power within the respiratory frequency band (0.12 to 0.40 Hz; Berntson et al., 1997), which is a high frequency bandwidth used in as an indicator of parasympathetic activity (Porges, 1995). Higher HRV-HF_{mean} values denote greater parasympathetic activity, and higher HRV-HF_{SD} values denote greater intra-individual variability in HRV-HF levels across time during the ESM sampling period.

4.4.2. Heart rate (HR)

Heart rate is influenced by both sympathetic and parasympathetic branches of the autonomic nervous system and was assessed as a general index of cardiovascular activity. R-wave interval estimates in milliseconds from the ECG signal were obtained using AcqKnowledge v3.9. Inter-beat interval (IBI) values were derived from this as the time between successive R-peaks of the ECG in milliseconds. IBI values were subsequently processed in MindWare HRV v.3.0 software module that converted these values to HR measured as beats per minute.

4.4.3. Respiration rate (RESP)

Respiration frequency as breathing cycles per minute was measured using a respiration belt transducer around the abdominal region using the Zephyr™ BioHarness™ device that measured breathing cycles per minute. Data were subsequently analyzed offline using AcqKnowledge v3.9 analysis software that converted respiration peak frequency to breaths per minute. All respiratory frequencies were examined to ensure they were within the designated respiratory frequency band (i.e., 0.12 Hz–0.40 Hz).

4.4.4. Skin temperature (SKT)

SKT was assessed as a broad measure of sympathetic nervous system activity. Blood vessels at the fingertip are innervated by sympathetic nerves (Schmidt & Thews, 1993), constricting with the increased and dilating with decreased sympathetic activity. Greater sympathetic activation leads to decrease in diameter of blood vessels at the fingertip, leading to decreased blood volume and decreased SKT. SKT was measured continuously using a thermistor attached to the Zephyr™ BioHarness™ device in the upper thoracic region of the abdomen. Voltage measurements obtained using the thermistor were converted offline using AcqKnowledge v3.9 software into degrees Fahrenheit.

4.4.5. Gross somatic movement (GSM)

We quantified gross physical movement as a potential confound in the present analyses, and was calculated offline as the sum of three accelerometer channels in three-dimensional (X, Y, and Z coordinate) space recorded on the Bioharness device. It was quantified using Mindware BSA v3.0.4 software's "total wiggle factor" variable by taking an ac type signal, full wave rectifying it using the absolute value and applying a low pass filtering to get the linear envelope and the integrating the area under the curve of this envelope. Units are measured in volts/second whereby higher values reflect greater gross somatic movement.

4.5. Procedure

The study procedure had four stages. First, participants arrived at the laboratory and provided written and verbal informed consent. Participants then underwent a diagnostic assessment interview to confirm diagnosis and remitted mood status using the YMRS (≤ 7) and IDS-C (≤ 11). Second, after completing an unrelated set of laboratory tasks, participants were invited to participate in the ESM study protocol over the subsequent week (e.g., Monday through the following Monday). Interested participants went through a training and acclimatization session (day 0) that

included wearing the Bioharness device and receiving a review of relevant ESM self-report items (for full results of self-report ESM items, see Gruber et al., 2013a, 2013b). Participants were advised to wear the Zephyr™ BioHarness™ device each day from 9 am to 6 pm except when showering or swimming, and were instructed on how to turn the device off and charge it overnight. Participants were encouraged to contact the experimenter if any questions arose outside the lab. Third, participants completed six consecutive days of the ESM protocol (days 1–6). Fourth, participants came back to the lab to return equipment and be debriefed, and current symptoms were reassessed to ensure that remitted mood was maintained.

4.6. Data analytic approach

Descriptive analyses consisting of one-way group ANOVAs followed by planned pairwise comparisons (BD group versus each other group) were first performed to characterize the diagnostic groups in terms of the various dependent measures. Then, hypotheses associated with Aims 1 and 2 were tested using group (BD, MDD, CTL) comparisons and continuous score correlations, respectively. The groups analyses consisted of planned pairwise comparisons evaluating differences for the HRV-HF_{mean} and HRV-HF_{SD} variables, with the BD group contrasted against the other two groups (Aim 1), and omnibus one-way ANOVAs for the secondary physiological variables (HR, RESP, SKT, and GSM). The continuous scores analyses focused on clinician-reported symptoms of mania (BRMS) and depression (IDS-C) (Aim 1), and state (mean state mDES-PA) and trait (mean trait mDES-PA) measures of positive affectivity administered to participants in all groups (Aim 2).

5. Results

5.1. Descriptive analyses

As seen in Table 1, BD, MDD, and CTL participants did not differ significantly with respect to age, gender, or ethnicity. All groups also scored well below standardized cutoffs on the BRMS and IDS-C scores. The BD and MDD groups both scored higher than the CTL groups on subsyndromal depressive symptoms, but did not differ from each other. Clinician-rated symptoms of mania assessed via the BRMS differed across the groups, $F(2,63) = 3.616, p = .03$ partial $\eta^2 = .103$, with pairwise comparisons revealing significant differences between BD ($M = 2.29, SD = 2.19$) and CTL groups ($M = 1.04, SD = 1.04, p = .009$), but not between BD and MDD groups ($M = 1.59, SD = 1.54, p = .189$). For the IDS-C, the omnibus test was not significant, $F(2,55) = 1.768, p = .180$, but planned pairwise comparisons found depression symptoms significantly higher in the BD group ($M = 5.00, SD = 2.69$) versus the CTL group ($M = 1.75, SD = 1.86, p = .005$). The BD group did not differ from the MDD group ($M = 5.29, SD = 2.69, p = .82$) on IDS-C. The BD group scored lower on global functioning (GAF) than the MDD and CTL groups, and the MDD group also scored lower than the CTL group on GAF scores.

We also sought to characterize the DSM-IV-defined groups (i.e., BD, MDD and healthy control) in terms of RDoC dimensions of subjective positive affectivity. Groups differed significantly on trait positive affectivity as measured by the trait version of the mDES PA scale, $F(2,56) = 3.409, p = .04$, partial $\eta^2 = .11$. Pairwise comparisons revealed no significant difference between the BD group ($M = 3.25, SD = .60$) and either the MDD ($M = 2.98, SD = .64, p = .205$) or the CTL group ($M = 3.53, SD = .75, p = .253$). Post-hoc comparisons using least significant difference revealed only one significant difference, between CTL and MDD ($p = .012$). There was also a trend for groups as a whole to differ in state positive affectivity as measured by averaging across the 24 experience-sampling assessments using the state version of the mDES scale i.e., state PA mean across 24 beeps sampled during the ESM study, $F(2,63) = 3.265, p = .045$, partial

$\eta^2 = .094$ – but in this case pairwise comparisons for the BD group versus the other groups were not significant.

5.2. Hypothesis testing

Aim 1: Group differences in HRV-HF. As summarized in Table 2, groups did not differ in either mean or SD scores for HR, RESP, SKT or GSM. They also did not differ in mean HRV-HF, but as expected, groups did differ in HRV-HF_{SD}, $F(2,61) = 3.997$, $p = .02$, partial $\eta^2 = .12$. One outlier was identified in this analysis (Z -score = 3.29), and this case was removed before planned comparisons were conducted for hypothesis testing. After removal of this outlier, pairwise comparisons revealed that HRV-HF_{SD} was higher in the BD group than either the CTL ($= 0.38$, $p = .004$) or the MDD group ($= 0.32$, $p = .035$). (See Table 3.)

In addition, the analysis of continuous BRMS symptom scores across all participants revealed a significant bivariate correlation for overall level of manic symptoms with HRV-HF_{SD}, $r = .27$, $p = .031$. To clarify the basis of the observed association between HRV-HF_{SD} and BRMS symptom scores, we examined bivariate correlations between HRV-HF_{SD} and each of the individual 11 BRMS items. Two specific items showed significant association with HRV-HF_{SD}: elevated mood ($r = .30$, $p = .014$) and self-esteem ($r = .32$, $p = .008$). In addition, to examine whether variations in manic symptoms accounted for diagnostic group differences in HRV-HF_{SD}, we performed a hierarchical regression analysis in which comparison physiological variables (means of HR, RESP, SKT, and GSM, as well as HRV-HF_{mean}) were entered as predictors in step 1, followed by diagnostic group (coded via dummy variables) in step 2, followed by BRMS symptom score in step 3. The entry of BRMS score in step 3 rendered the effect of diagnostic group (which was robust at step 2) nonsignificant.

Aim 2: Dimensional measures of positive affectivity and HRV-HFSD. Predicted associations for mDES trait PA, and average state PA with HRV-HF_{SD}, were all non-significant ($r = .19$, $p = .147$; $r = .13$, $p = .312$, respectively).

6. Discussion

The present investigation used an ecologically valid and rigorous approach to assess naturalistically occurring variation in physiological measures hypothesized to index positive emotional disturbance, namely, mean levels and variation in HRV-HF. The study also included measurement of important comparison variables consisting of general cardiovascular arousal, sympathetic nervous system activity, and gross somatic movement. Participants were adults from the community with diagnostic conditions presumed to reflect PVS disturbances (i.e., BD and MDD) along with a healthy non-psychiatric control group. This study was unique in combining a real-world perspective with a broad, theoretically driven conceptualization of PVS and testing for effects of both disorder categories and continuous measures of symptoms and positive affective tendencies. Findings from this work provide an important complement to laboratory investigations that have thus far dominated our understanding of PVS and physiological response as related to clinical mood disturbance.

The first aim was to test whether DSM-IV-defined groups differed in RDoC dimensions of positive affectivity as indexed by HRV-HF_{SD}. Consistent with the HRV-HF instability hypothesis, the BD group exhibited higher HRV-HF_{SD} compared to both the MDD and CTL groups. This finding converges with previous laboratory and questionnaire studies of self-reported positive affectivity suggesting that BD spectrum disorders are associated with greater self-reported variability in positive emotional experience (Lovejoy & Steuerwald, 1995) and that higher self-reported emotion variability is related to a greater level of depressive

symptoms in BD (Bonsall et al., 2012) and non-clinical populations (Gruber et al., 2013a, 2013b). Importantly, this finding also converges with more basic science perspectives on PVS functioning which suggest that instability in positive affectivity is associated with greater psychological health disturbance across a range of clinical measures such as increased depressive symptoms, increased anxiety symptoms, and decreased life satisfaction (Gruber et al., 2013a, 2013b).

Such findings also highlight the value of examining intra-individual variability in physiological measures across time, in addition to overall levels of activity or responding, to gain a more complete understanding of the dynamic nature of positive affectivity (Davidson, 1998) and its relationship to clinically relevant RDoC dimensions of affectivity (e.g., Cuthbert & Kozak, 2013; Cuthbert & Insel, 2013; Insel et al., 2010; Sanislow et al., 2010). Specifically, the present findings suggest that too much variability within a putative parasympathetic indicator of positive emotional functioning is associated with a greater likelihood of a clinical diagnosis of BD, a disorder marked by severe and persistent disturbances in positive emotion (e.g., Gruber, 2011; Johnson, 2005). Future work is needed to systematically probe whether different types of variability – such as frequent yet small oscillations in HRV-HF versus infrequent but large oscillations in HRV-HF – predict different psychological-health trajectories relevant to PVS. Indeed, unstable compared to stable HRV-HF may be harmful because it involves extreme lows and highs, both of which have been shown to be maladaptive across psychological and also physical health outcomes (Gruber et al., 2011c, 2013a). In addition it will be important to examine the extent to which variation in HRV-HF may be representative of more broad based differences in affective-regulatory capacity (e.g., Beauchaine, 2001; Beauchaine, 2012; Beauchaine & Gatzke-Kopp, 2012) that spans disturbances in both positive and negative valence systems.

Importantly the findings appeared specific to HRV-HF_{SD}, as the diagnostic groups did not differ in mean levels of HRV-HF or in indices of general cardiovascular arousal, sympathetic activity, and gross somatic movement. This suggests that the observed group differences were not merely driven by extreme lows or highs of HRV-HF, or by general physiological activation (or lack thereof), but rather by the simultaneous occurrence of lows and highs in HRV-HF across time. Furthermore, the group differences in HRV-HF_{SD} held when controlling for relevant psychophysiological confounds including mean HRV-HF, heart rate, respiratory frequency, and gross somatic movement – further highlighting the specificity of HRV-HF_{SD} and its association with disorders of heightened positive emotionality such as BD. This finding has implications for translational interventions aimed at promoting psychophysiological health, suggesting that interventions may be most successful when they incorporate noninvasive, real-world indices of physiological functioning and focus on reducing variability in such measures as opposed to solely focusing on enhancing HRV-HF levels.

Notably, we also found that clinician-rated mania symptoms assessed using the BRMS were significantly associated with increased HRV-HF_{SD} across all participants. Further, we found in a hierarchical regression analysis that the association for BD diagnosis with HRV-HF_{SD} fell to non-significance when the BRMS dimensional-symptom measure was included as a concurrent predictor. Although theoretically linked to pathologically elevated positive affectivity, the clinical syndrome of mania in BD is multi-faceted, including symptoms spanning increased agitation, sleep disturbance, and distractibility (e.g., Johnson et al., 2012). Moreover, all study participants were remitted at the time of testing, so only subsyndromal manic characteristics were quantified here. Given these considerations, we sought to clarify the observed association between this dimensional measure of manic symptoms and HRV-HF variability by examining associations for individual items of the BRMS. This follow-up analysis revealed that two specific items showed significant associations with HRV-HF_{SD}. These items, elevated mood and self-esteem, can be considered to be relatively specific to state positive affectivity. While this appears consistent with our expectation that the HRV-HF variable would correlate with dimensional

Table 2
Descriptive statistics for ambulatory physiology variables dimensionally across All participants and by diagnostic group during the six day experience sampling period.

Domain	Group			All (n = 66)	Statistic
	BD (n = 21)	MDD (n = 17)	CTL (n = 28)		
<i>Parasympathetic activity (index of positive valence system activity)</i>					
HRV-HF _{Mean}	7.60 (0.24)	7.71 (0.38)	7.59 (0.24)	7.63 (0.16)	$F(2,63) = 0.05, p = 0.96, \text{partial } \eta^2 = 0.00$
HRV-HF _{SD}	1.44 (0.10)	1.23 (0.14)	1.06 (0.08)	1.22 (0.06)	$F(2,61) = 4.00, p = 0.02, \text{partial } \eta^2 = 0.12$
<i>Cardiovascular arousal</i>					
HR _{Mean}	84.71 (1.78)	82.82 (2.22)	84.46 (1.95)	84.96 (1.15)	$F(2,63) = 0.81, p = 0.45, \text{partial } \eta^2 = 0.03$
HR _{SD}	14.39 (1.86)	11.52 (1.01)	15.14 (2.00)	13.97 (1.07)	$F(2,63) = 0.95, p = 0.39, \text{partial } \eta^2 = 0.03$
RESP _{Mean}	18.78 (0.51)	17.66 (0.58)	18.89 (0.25)	18.54 (0.25)	$F(2,63) = 2.29, p = 0.11, \text{partial } \eta^2 = 0.07$
RESP _{SD}	2.06 (0.21)	1.76 (0.09)	2.11 (0.16)	2.00 (0.10)	$F(2,63) = 1.08, p = 0.35, \text{partial } \eta^2 = 0.03$
<i>Sympathetic activity</i>					
SKT _{Mean}	94.53 (0.38)	94.93 (0.31)	94.21 (0.32)	94.50 (0.20)	$F(2,63) = 1.06, p = 0.35, \text{partial } \eta^2 = 0.03$
SKT _{SD}	2.87 (0.45)	2.30 (0.47)	2.70 (0.31)	2.65 (0.23)	$F(2,63) = 0.46, p = 0.64, \text{partial } \eta^2 = .01$
<i>Gross somatic movement</i>					
GSM _{Mean}	0.22 (0.02)	0.24 (0.02)	0.25 (0.01)	0.24 (0.01)	$F(2,63) = 1.18, p = 0.31, \text{partial } \eta^2 = 0.04$
GSM _{SD}	0.48 (0.34)	2.57 (0.95)	1.33 (0.56)	1.40 (0.37)	$F(2,61) = 2.42, p = 0.10, \text{partial } \eta^2 = 0.07$

Note: BD = bipolar I disorder group; MDD = major depressive disorder group; CTL = healthy control group; HRV-HF = high frequency heart rate variability (0.12 to 0.40 Hz); HR = heart rate (measured in beats per minute); SKT = skin temperature (measured in degrees Fahrenheit); GSM = gross somatic movement in three-dimensional space measured in volts/second. Means sharing a superscript letter (a, b or c) were significantly different in specific group comparisons ($p < .05$). Standard values (between-group) are included in parentheses.

measures of positive affectivity, the complexity of the measure remains a limitation.

Moreover, in analyses directed at addressing Aim 2 of the study, we found that dimensional measures designed specifically to index positive affectivity, consisting of state as well as trait PA scales of the mDES, did not correlate significantly with HRV-HF instability (i.e., HRV-HF_{SD}). This result, which is contrary to a priori hypotheses, could have differing explanations. One possibility is that manic symptoms entailing elevated mood and exaggerated self-esteem may reflect an aspect of PVS function distinct from the content of normative PA scales, which relates more to HRV-HF. An alternative but not incompatible possibility is that the relationship that manic symptoms show with HRV-HF reflects affective-regulatory dysfunction more so than PVS dysfunction per se (e.g., Beauchaine, 2012; Beauchaine & Gatzke-Kopp, 2012). Yet another possibility is that report-based PA scales are limited in terms of tapping aspects of PVS function that are most relevant to clinical problems. Consistent with the aims of the RDoC initiative, it will be important in future work to establish reliable and effective criterion measures of PVS processes based on measurement sources other than report.

Table 3
Hierarchical regression analysis predicting HRV-HF_{SD} across participants.

Model	Variable entered	Beta	t	Sig	R square change	Sig F change
1	HRV-HF mean	-.023	-.164	.870	.027	.919
	HR mean	.172	1.152	.255		
	RESP mean	-.059	-.374	.710		
	SKT mean	.062	.397	.693		
	GSM mean	.015	.097	.923		
2	BD	.338	2.545	.014*	.110	.014*
	BRMS	.450	3.292	.002**		
3 Final model	HRV-HF mean	-.018	-.141	.888	.154	.002**
	HR mean	.270	2.042	.046*		
	RESP mean	-.206	-1.450	.153		
	SKT mean	.096	.706	.483		
	GSM mean	-.084	-.616	.540		
	BD	.209	1.631	.109		
	BRMS	.450	3.292	.002**		

Note: BD = bipolar I disorder group; BRMS = Bech-Rafaelsen Mania Scale; HRV-HF = high frequency heart rate variability (0.12 to 0.40 Hz); HR = heart rate (measured in beats per minute); SKT = skin temperature (measured in degrees Fahrenheit); GSM = total wiggle factor (gross somatic movement in three-dimensional space measured in volts/second).

* $p < .05$.

** $p < .005$.

Although not part of our primary aims, we note that some aspects of the current results for HRV-HF_{mean} levels appear inconsistent with previous laboratory studies. Specifically, the BD group did not exhibit increased levels of mean HRV-HF compared to the MDD and CTL group. This finding diverges from laboratory studies suggesting that individuals at risk for, and diagnosed with, BD exhibit greater HRV-HF mean levels compared to healthy control or low-risk comparison groups (e.g., Gruber et al., 2008, 2011b). How might prior laboratory findings be reconciled with the present ESM data? One key distinction is that controlled laboratory environments minimize the influence of everyday emotional triggers and life events on HRV-HF, whereas the present data for HRV-HF were open to the real-world impact of everyday life events, physical health triggers, and life stressors during the ESM study period, all of which are known to influence mean HRV-HF levels (Grossman & Taylor, 2007). Indeed, individuals with BD may have a propensity toward heightened HRV-HF levels compared with healthy adults, all else being equal (e.g., Gruber, 2011).

Our findings should be interpreted within the confines of several limitations. First, the present findings relied on ambulatory measures of psychophysiology that were obtained using lower sampling rates (i.e., 250 Hz) given technological limitations of acquiring large data samples across a continuous six-day period. Although we acknowledge the limits of this in computing measures of HRV-HF which rely best on sampling rates > 1000 Hz (e.g., Berntson et al., 1995), we also believe these findings represent a critical first-step into exploring HRV-HF outside of the laboratory and providing impetus for future studies and technologies to conduct greater research in real-world settings that are not exclusively limited to self-report measurements. Second, we note that the present investigation sample from a population whose recruitment strategy relied on a traditional DSM-diagnostic sampling approach which precludes our ability to advance firm conclusions regarding how the obtained findings might inform a more dimensionally oriented RDoC approach (e.g., Cuthbert & Kozak, 2013; Cuthbert & Insel, 2013; Insel et al., 2010; Sanislow et al., 2010). At the same time, this study provides initial pilot investigation that highlights the promise of psychophysiological measures collected in real-world settings to provide key insights into dysfunctions in emotional systems that underlie clinical problems. It will be important for future studies to build upon these initial insights and to examine patterns of instability in parasympathetic activity in association with more dimensional assessments of both positive affectivity and clinically relevant mood outcomes.

Third, the present study did not explicitly assess the role of contextual factors such as everyday emotion eliciting events and life stressors,

which could have influenced the obtained findings. Future studies are thus needed to evaluate the possibility of interactions between situational context and physiological functioning. Third, we note that the present sample sizes are impressive given the severe nature of the psychiatric groups recruited and complexity of the measured variables. Nonetheless, it will be important to replicate these findings in even larger samples. Moreover, the fact that the present study included a clinical comparison group (i.e., MDD) along with a healthy control group to examine emotion difficulties within the mood disorder family represents a strength of the study and an important first step toward identifying shared-dimensional features across clinical conditions (e.g., Cuthbert & Kozak, 2013; Cuthbert & Insel, 2013; Insel et al., 2010; Sanislow et al., 2010). Fourth, given the challenges of accessing an unmedicated clinical sample, we were unable to investigate the influence of medication effects on observed results. However, future studies with larger sample sizes, assessment of blood serum levels, and random assignment of individuals on different medication classes are warranted. Finally, the current study was cross-sectional and thus unable to address hypotheses regarding how physiologically-relevant emotional profiles in everyday life predict the course of relapse and recurrence, highlighting a need for longitudinal designs.

Despite these limitations, the present study provides support for the potential of psychophysiology measurement to inform future research investigating clinically-relevant variation in the positive valence domain and emotional functioning more generally. Importantly, multi-study programs are required to comprehensively investigate hypothesized relationships among clinical conditions, dimensions of functioning, and physiological measures. As evidenced by its sampling strategy, our study's design prioritized diagnosis over dimensional measurement. Any conclusions drawn in this study therefore require corroboration in samples designed to capture the full range of positive emotional functioning. It will be important in future studies of this type to employ samples of sufficient size to permit sophisticated statistical modeling of relationships among states, traits, and physiological variables.

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