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Authors
Muhtadie, Luma
Johnson, Sheri L

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Threat Sensitivity in Bipolar Disorder

Luma Muhtadie

Department of Psychology, University of California, Berkeley

Sheri L. Johnson

Department of Psychology, University of California, Berkeley and Center for Advanced Study in the Behavioral Sciences, Stanford University

Abstract

Life stress is a major predictor of the course of bipolar disorder. Few studies have used laboratory paradigms to examine stress reactivity in bipolar disorder, and none have assessed autonomic reactivity to laboratory stressors. In the present investigation we sought to address this gap in the literature. Participants, 27 diagnosed with bipolar I disorder and 24 controls with no history of mood disorder, were asked to complete a complex working memory task presented as "a test of general intelligence." Self-reported emotions were assessed at baseline and after participants were given task instructions; autonomic physiology was assessed at baseline and continuously during the stressor task. Compared to controls, individuals with bipolar disorder reported greater increases in pretask anxiety from baseline and showed greater cardiovascular threat reactivity during the task. Group differences in cardiovascular threat reactivity were significantly correlated with comorbid anxiety in the bipolar group. Our results suggest that a multimethod approach to assessing stress reactivity—including the use of physiological parameters that differentiate between maladaptive and adaptive profiles of stress responding— can yield valuable information regarding stress sensitivity and its associations with negative affectivity in bipolar disorder.

Keywords

bipolar disorder; stress reactivity; psychophysiology; challenge; threat

Bipolar I disorder is a severely disabling mental illness characterized by episodic shifts in mood, energy levels, and functioning that can be devastating. Although bipolar disorder is known to be highly heritable (McGuffin et al., 2003), evidence also suggests that environmental stressors, including interpersonal conflicts, expressed emotion, and life events, can predict the onset of mood disorders, trigger episodes, and exacerbate the illness course (Hillegers et al., 2004; Johnson & Miller, 1997; Miklowitz, Simoneau, Sachs-Ericsson, Warner, & Suddath, 1996; Swendsen, Hammen, Heller, & Gitlin, 1995).

Beyond research demonstrating the influence of life stress on the course of bipolar disorder, several naturalistic studies also have suggested that individuals with this illness demonstrate

Correspondence concerning this article should be addressed to Luma Muhtadie, Department of Psychology, University of California, Berkeley, 3210 Tolman Hall, Berkeley, CA, 94720. lmuhtadie@berkeley.edu.

exaggerated emotional and physiological reactivity to daily stressors and hassles relative to nonpsychiatric controls (Havermans, Nicolson, Berkhof, & deVries, 2010, 2011; Myin-Germeys et al., 2003). However, very few studies have experimentally manipulated stress in the laboratory, and the existing ones have yielded somewhat mixed findings.

In the only past study to examine physiological parameters of reactivity to a laboratory stressor in bipolar spectrum disorder, Depue, Kleiman, Davis, Hutchinson, and Krauss (1985) observed a pattern of cortisol hypersecretion and high intra-individual variability of cortisol levels before, during, and after a math challenge among individuals with cyclothymia relative to nondisordered controls (Depue et al., 1985). There are several caveats worth noting here. First, this study focused on cortisol responses, which reflect the activity of the hypothalamic-pituitary-adrenal (HPA) axis; no studies of bipolar spectrum disorder have examined acute stress reactivity using autonomic parameters, which reflect the quick and highly responsive activity of the sympathetic-adrenal-medullary system to unanticipated stressors (Mendes & Jamieson, 2012). Second, given that group differences in cortisol responding in the Depue and colleagues study were observed before the onset of the stressor, these findings suggest a more chronic underlying pattern of HPA axis dysregulation, as opposed to reactivity to the laboratory stressor per se. Finally, the aforementioned study included a sample of individuals with cyclothymia rather than the more severe diagnosis of bipolar I disorder.

In terms of studies focusing specifically on individuals diagnosed with bipolar I disorder, Ruggero and Johnson (2006) reported heightened cognitive reactivity to stress among bipolar individuals in full or partial remission relative to controls, but found no differences in self-reported emotional reactivity between the two groups. By contrast, Cuellar, Johnson, and Ruggero (2009) reported a trend toward greater self-reported emotional reactivity in response to criticism among bipolar individuals relative to controls. A crucial point is that no laboratory study to date has examined physiological parameters of stress reactivity in bipolar I disorder.

Biopsychosocial Theory of Challenge and Threat

The present study draws on a well-validated approach to understanding stress responses and their associated cardiovascular profiles. The biopsychosocial theory of challenge and threat differentiates between two distinct motivational states that are elicited when people are expected to perform. For challenge and threat processes to unfold, stressors must be perceived as goal relevant and evaluative; in other words, the task in question must pertain to a valued or self-relevant domain and require instrumental cognitive responses that will be evaluated by the self or others, thereby eliciting engagement (Blascovich & Mendes, 2000). Assuming task engagement, whether individuals experience states of challenge or threat depends on their perceptions and appraisals of the relative balance between the demands of a task and the personal resources available to them (Blascovich & Mendes, 2000). Whereas challenge appraisals arise when individuals perceive themselves as having adequate personal resources to cope with the demands of a task, threat appraisals arise when individuals perceive the situational demands to exceed their personal coping resources.

Beyond these cognitive appraisals, which can occur consciously or nonconsciously, challenge and threat states also encompass emotional and physiological responses. At the level of experienced emotion, challenge has been associated with confidence and threat with anxiety (Blascovich & Mendes, 2000; Mendes, McCoy, Major, & Blascovich, 2008; Skinner & Brewer, 2002). In terms of cardiovascular responses, more than 30 published studies have established that challenge states are accompanied by a cardiovascular profile characterized by increases in cardiac efficiency and decreases in vascular resistance—a constellation of responses enables greater blood supply to the brain and periphery, preparing the body for action. Threat states are accompanied by an inverse profile of cardiovascular responses—namely, decreases in cardiac efficiency and increases in vascular resistance—a pattern that likely evolved to prepare the body for damage and defeat (Blascovich & Mendes, 2000; Kassam, Koslov, & Mendes, 2009; Mendes, Blascovich, Hunter, Lickel, & Jost, 2007). Past studies have shown that cardiovascular challenge predicts better performance than does cardiovascular threat, and this predictive power is better than with any other single cardiovascular measure (Blascovich, Seery, Mugridge, Norris, & Weisbuch, 2004; Seery, Weisbuch, Hetenyi, & Blascovich, 2010; Weisbuch, Seery, Ambady, & Blascovich, 2009). Thus, threat states can be viewed as less adaptive in the context of goal pursuit.

Although past research has not tested the relative tendencies of individuals with bipolar disorder to experience challenge versus threat, there is reason to suspect that people with this disorder would be particularly vulnerable to experiencing threat and its concomitant emotional and cardiovascular profile. First, a large body of theory has characterized bipolar disorder as involving stress reactivity (e.g., Phillips, Drevets, Rauch, & Lane, 2003; Strakowski, 2012; Strakowski et al., 2012). Second, studies of representative samples have found that as many as 60% of individuals with bipolar disorder have at least one anxiety disorder (Bauer et al., 2005; Boylan et al., 2004; Mantere et al., 2006; Mitchell et al., 2013; Otto et al., 2006; Simon et al., 2004) and many people with bipolar disorder continue to experience residual depressive symptoms during interepisode periods. Both anxiety disorders and depressive symptoms have been associated with threat sensitivity (Britton, Lissek, Grillon, Norcross, & Pine, 2011; Meyer, Johnson, & Winters, 2001).

The Present Study

In the present investigation, we compared self-reported emotions and cardiovascular responses to a motivated performance task among individuals diagnosed with bipolar I disorder and a well-matched control group of individuals with no history of mood disorder. Participants were asked to complete a timed, computer-based complex working memory task. To increase the goal relevance of this task (and thus, participant engagement), it was presented as “a test of thinking and memory that has been robustly associated in past studies with general intelligence.” This framing was chosen because intelligence is considered to be a core attribute of the self-identity that is widely valued (Dickerson & Kemeny, 2004). We hypothesized that individuals with bipolar disorder would experience greater threat reactivity than would controls in response to this goal-relevant stressor. In particular, we hypothesized that in the face of this stressor, bipolar participants would report greater increases in pretest anxiety and exhibit a cardiovascular reactivity profile characterized by decreases in cardiovascular efficiency and increases in vascular resistance.

Method

Participants

Participants were 27 individuals who met criteria for bipolar I disorder (interepisode period), as assessed by the Structured Clinical Interview for *DSM–IV* for Axis I disorders (SCID–I; First, Gibbon, Spitzer, & Williams, 1996) and 24 control individuals with no lifetime history of mood disorder (CTL). Participants were recruited through advertisements placed on the Internet and on flyers posted in the community and at local outpatient clinics. Participants in the bipolar group met the Diagnostic and Statistical Manual of Mental Disorders (4th ed.; *DSM–IV*; American Psychiatric Association, 1994) diagnostic criteria for bipolar I disorder, and those in the control group did not meet lifetime or current criteria for any mood disorder (i.e., bipolar spectrum disorder, major depressive disorder, dysthymia). All participants were primary English speakers aged 18 to 59 years. Individuals were excluded if they met *DSM–IV* diagnostic criteria for a primary psychotic disorder during their lifetime; had substance abuse or dependence in the past 6 months; or had any neurological disorder, history of head injury with loss of consciousness, or any developmental or language disability that would impede their ability to provide informed consent or understand study tasks or measures.

Individuals also were screened for conditions that altered cardiovascular responding, including physician-diagnosed hypertension, heart murmur, presence of a pacemaker or other implanted cardiovascular device, use of medications affecting cardiovascular system responses (e.g., beta-adrenergic blocking agents), and pregnancy. In addition, individuals with a body mass index over 35 were excluded because of difficulties this posed to obtaining reliable impedance cardiography data. Participants provided verbal consent before the telephone-screening interview and completed written informed consent procedures before taking part in the study procedures. All participants were paid for their time, and all procedures were in compliance with the Institutional Review Board at the University of California.

Diagnostic Assessment

The SCID–I is a commonly used and well-validated semistructured interview used to make current and lifetime psychiatric diagnoses based on *DSM–IV* criteria (First et al., 1996). All interviewers were graduate students in clinical psychology who received extensive didactic and role-play training in SCID–I procedures, and who had previous diagnostic experience with psychiatric populations. Reliability ratings were conducted throughout the duration of the study. Four judges independently rated 10 randomly selected audiorecorded interviews. Intraclass correlations for ordinal data were used to assess reliability of diagnostic judgments using absolute agreement as the criterion. Interrater reliabilities for all diagnostic categories in this study were excellent: intraclass *r*s = .89 for the presence of lifetime and current mania, and .99 and .96 for the presence of lifetime and current major depressive episode, respectively. Interrater reliability for number of lifetime symptoms was also high, intraclass *r*s = 1.0 for mania and .99 for depression. To examine the potential role of comorbid anxiety, participants were screened for several anxiety disorders—namely, specific phobia, panic disorder, agoraphobia, social anxiety disorder, obsessive– compulsive

disorder, posttraumatic stress disorder, and generalized anxiety disorder—and dichotomous scores were computed for the presence or absence of any of these disorders.

Assessment of Mood Symptoms

The Beck Depression Inventory–Short Form (BDI–SF; Beck, Rush, Shaw, & Emery, 1979) is an abbreviated 13-item version of the self-report Beck Depression Inventory (BDI). Correlations between the short and long forms of the BDI have ranged from .89 to .97 (Beck, Steer, & Garbin, 1988). Items and response options for the BDI–SF are taken from the original instrument and assess symptoms such as sadness, anhedonia, hopelessness, indecisiveness, loss of energy and appetite, guilty feelings, and suicidal thoughts during the past 2 weeks. For each item, four response options are given on a 0 to 3 scale provide increasingly severe descriptions of the target symptom (e.g., for sadness: 0 = *I do not feel sad*; 3 = *I am so sad or unhappy that I can't stand it*). The BDI–SF had good internal consistency in the present sample, $\alpha = .85$.

The Altman Self-Rating Mania Scale (ASRM; Altman, Hedeker, Peterson, & Davis, 1997) is a five-item self-report questionnaire that assesses the presence and severity of manic symptoms within the past week. The ASRM items measure increased cheerfulness, inflated self-confidence, talkativeness, reduced need for sleep, and excessive behavioral activity. For each item, five response options are given on a 0 to 4 scale provide increasingly severe descriptions of the target dimension (e.g., for sleep: 0 = *I do not need less sleep than usual* and 4 = I can go all day and night without any sleep and still not feel tired). The ASRM has been found to be sensitive to changes in clinical state, to differentiate mania from other clinical conditions, and to be low in participant burden (Altman et al., 1997). The ASRM had acceptable internal consistency in the present sample, $\alpha = .73$.

Medications

To consider the potentially confounding associations between psychotropic medications and emotional and cardiovascular outcomes, levels of five classes of medications—lithium, second-generation antipsychotics, anticonvulsants, lamotrigine, and anti-depressants—were coded using the Somatotherapy Index (Bauer et al., 1997), an interview-based rating system that incorporates information on prescribed dosages and adherence rates to estimate dose equivalence. All second-generation antipsychotics were converted to a dose equivalency for risperidone and all antidepressants were converted to a dose equivalency for imipramine. Dosages for the medications in all five classes were adjusted by multiplying the prescribed dose equivalency of each drug by the reported adherence rate. The three first-line antimanic agents (lithium, second-generation antipsychotics, and anticonvulsants) were combined to form a single composite mood stabilizer score. Because the maximum prescribed dosages of these three medications are very different from each other, we scaled the levels by computing the proportion of the maximum prescribed dosage actually taken (i.e., prescribed dose multiplied by adherence rate, divided by maximum dose) then added the resulting values for all three drugs for each participant. The resulting mood stabilizer dose level was used in subsequent analyses, alongside antidepressant and lamotrigine dose levels.

Working Memory

The Automated Symmetry Span Task is a widely used and well-validated computer-based complex working memory paradigm. This task served as the laboratory stressor and was presented as "a test of general intelligence" to increase its goal-relevance. In this paradigm, participants are presented with a 4 × 4 grid on which a red square flashes in different positions, and they are instructed to attend to and remember the serial positions in which the red square appeared. Before taking a recall test, participants complete an intervening task in which they see a design and are asked to judge whether it is symmetrical. Participants thus are required to shift their attention between two task components: (1) a storage component requiring them to encode the location of a red square that appears in various positions on a 4 × 4 grid; and (2) a processing component requiring them to judge whether a design is symmetrical about its vertical axis. These two components are interleaved, requiring participants to concurrently store and actively manipulate information in working memory thereby posing a high level of cognitive demand. Participants completed 42 trials, which took approximately 3 min. Scores reflect the total number of items recalled on the storage portion of the task. Given that robust cognitive deficits have been widely reported in individuals with bipolar I disorder, even during remission (Arts, Jabben, Krabbendam, & van Os, 2008; Bora, Yucel, & Pantelis, 2009; Robinson et al., 2006), and given that pre/posttesting could not be conducted due to the strong practice effects associated with complex working memory span tasks (Barch et al., 2009), the task was simply used as a way to engender stress and allow us to examine challenge and threat responses; task performance was not a focal point of our investigation.

Self-Reported Emotions

At the outset of the session and again after receiving the task instructions, participants were prompted to "rate the extent to which you feel this way right now" on eight different emotion terms (enthusiastic, frustrated, content, excited, anxious, irritated, sad, and confident). Ratings were made using a 5-point Likert scale ranging from 1 (*very slightly* or *not at all*) to 5 (*a lot*). Our analyses focused on two central emotions: anxiety and confidence, as indexes of threat and challenge, respectively.

Cardiovascular Physiology

Heart rate (HR), pre-ejection period (PEP), cardiac output (CO), mean arterial pressure (MAP), and total peripheral resistance (TPR) were assessed. ECG, impedance cardiography (ZCG; Biolab acquisition system; Mindware Technologies, Gahanna, OH), and blood pressure (Colin Prodigy II, Colin Medical Instruments, San Antonio, TX) were acquired during a 5-min baseline period at the outset of the session and throughout the cognitive test. All physiological signals were recorded at a sampling rate of 1 kHz. ECG was recorded continuously with spot electrodes placed on participants' torsos in a modified lead II configuration. ZCG was recorded continuously using four spot electrodes placed at the manubrium, xiphisternal junction, nape of the neck, and lower back. Blood pressure was measured at 1-min intervals during baseline and throughout the cognitive test.

ECG and ZCG signals were scored offline by visual inspection in 1-min epochs and analyzed using Mindware software (HRV and impedance scoring modules; Mindware

Technologies, Gahanna, OH). For each channel of physiology (HR, PEP, CO, MAP, TPR), responses across the full 5-min baseline period were averaged to yield a mean baseline value. HR was calculated from the R–R intervals in the ECG. PEP was identified as the time elapsed between the Q-point on the ECG wave (left ventricle contracting) and the B-point on the ZCG wave (aortic valve opening). CO was calculated by first estimating stroke volume (the amount of blood ejected during each beat) then multiplying stroke volume by HR. TPR was derived from the equation: MAP × 80/CO.

Consistent with previous literature, PEP was scored and examined as an index of task engagement, which is a precondition for the analysis of challenge and threat profiles (Mendes, Reis, Seery, & Blascovich, 2003). *PEP*, provides a pure measure of sympathetic nervous system influence on the heart. Increases in sympathetic nervous system activation are reflected in significant decreases in PEP from baseline (Brownley, Hurwitz, & Schneiderman, 2000) and indicate task-related arousal that would be expected with engagement. Thus, although PEP is crucial for ascertaining task engagement, it does not convey whether the type of stress experienced, as indexed by cardiovascular response, was adaptive or maladaptive to the situation at hand; this is where the assessment of challenge versus threat comes in.

Our core hypothesis focused on a single index of cardiovascular threat reactivity that combines CO and TPR. CO is a measure of the amount of blood (in liters) ejected from the heart during 1 min and provides an index of cardiac efficiency; TPR is a measure of the net constriction versus dilation in the arterial system and provides an index of vascular resistance. Following past research, we created this cardiovascular threat reactivity index by summing CO and TPR after standardizing the indicators and reverse-coding CO (because greater CO values indicate less threat). A considerable body of literature supports combining CO and TPR reactivity into a single challenge/threat index, given that both components track the same underlying pattern of physiological activation (Murray, Lupien, & Seery, 2012). Although this yields only relative threat differences—losing the absolute meaning of TPR and CO— it allowed us to assess the pattern of cardiovascular reactivity in a single analysis (Blascovich et al., 2004; Seery, Weisbuch, & Blascovich, 2009; Seery et al., 2010; Shimizu, Seery, Weisbuch, & Lupien, 2011; Townsend, Major, Sawyer, & Mendes, 2010).

Procedure

Participants began the experimental session by completing baseline measures of emotion. Physiological sensors were then applied and participants sat upright in a comfortable chair for a 5-min recording of their baseline physiology. Next, participants were presented with the working memory task, which they were told was “a test of thinking and memory that past studies have found to be a highly reliable measure of general intelligence.” Immediately after being given this information, but before beginning the task, participants were asked to complete the emotion ratings again to enable assessment of their emotional reactivity to this goal-relevant stressor. Participants then completed the working memory task while their autonomic physiology was measured continuously. At the end of the task, physiological sensors were removed and participants were verbally debriefed and compensated.

Data Analysis Plan

First, to assess potential baseline differences in self-reported emotion or physiology between the bipolar and control groups, group differences in self-reported emotion (anxious, confident) and cardiovascular responses (HR, PEP, CO, MAP, TPR) were tested. Next, to assess whether our manipulation had engendered sufficient task engagement and stress arousal in the two groups—a necessary precondition for examining challenge and threat responses— changes in PEP from baseline were tested within each group. To test our core hypotheses that individuals with bipolar I disorder would show greater threat reactivity to the evaluative stressor than would controls, the groups were compared on the following parameters: (1) changes in self-reported emotions of anxiety and confidence from baseline on receiving the task instructions, and (2) changes in cardiovascular threat reactivity from baseline during the task. Finally, follow-up analyses were performed to rule out the potentially confounding effects of comorbid anxiety and psychotropic medications on emotional and physiological reactivity. All analyses were conducted using SPSS version 22.0.

Results

Preliminary analyses indicated that all outcome variables were normally distributed according to established cut-offs of an absolute value of 1.5 for skewness and kurtosis, and we reviewed plots for potential outliers before conducting analyses.

Sample characteristics are presented in Table 1. Descriptive data **T1** indicate that there were no significant differences between the bipolar and control groups in age, gender, BMI, and current manic symptom scores. Participants in the bipolar group had a fairly severe illness history and reported significantly higher levels of depressive symptoms, but the group mean was still well below the established clinical cut-off score of nine out of a maximum possible score of 39 (Furlanetto, Mendlowicz, & Bueno, 2005) for this measure. Individuals in the bipolar group also had a significantly higher rate of comorbid anxiety disorders than did those in the control group (37% and 0%, respectively). More specific, two individuals had a diagnosis of social anxiety disorder; three had a diagnosis of posttraumatic stress disorder; one had panic disorder and social anxiety disorder; one had social anxiety disorder and generalized anxiety disorder; one had obsessive– compulsive disorder and posttraumatic stress disorder; and one had panic disorder, social anxiety disorder, and obsessive–compulsive disorder.

Consistent with previous findings on cognitive functioning in bipolar disorder, there was a significant difference in complex working memory performance between the two groups, $t(49) = 2.63$, $p = .009$, Cohen's $d = 0.76$, with the bipolar group performing worse, $M = 23.78$, $SD = 7.26$, than did the control group, $M = 29.43$, $SD = 7.55$.

Were the Bipolar and Control Groups Well Matched at Baseline (Before the Stress Manipulation)?

There were no differences between the bipolar and control groups on any of the self-reported emotions at baseline, all ts < 0.49, all ps > .624. There also were no differences

between the bipolar and control groups on any of the physiological parameters (HR, PEP, CO, MAP, TPR) at baseline: all *t*s < 1.47, all *p*s > .142.

Did the Manipulation Engender Task Engagement in the Two Groups?

To test whether we had engendered task engagement, changes in PEP were examined within each group using dependent *t* tests comparing PEP values during the stressor against baseline PEP values. Significant decreases in PEP from baseline were observed in both the bipolar group, $M = -7.14$, $t(26) = 39.82$, $p < .001$, 95% CI [−9.61, −4.67], and the control group, $M = -8.00$, $t(23) = 47.83$, $p < .001$, 95% CI [−10.48, −5.52], confirming that we were successful in eliciting sympathetic activation—a marker of general arousal and a precondition for assessing challenge and threat responses.

Did the Bipolar and Control Groups Differ in their Emotional Reactivity to the Stressor?

To assess changes in self-reported emotions as a result of the manipulation, difference scores were calculated by subtracting participants' baseline reports of confidence and anxiety from their self-reported confidence and anxiety on receiving the task instructions (i.e., that they would be completing an intelligence test). Results indicated no significant difference between the bipolar and control groups on changes in confidence, $t(49) = 1.30$, $p = .194$, but the bipolar group showed significantly greater increases in anxiety, $M = 1.24$, $SD = 1.29$, than did the control group, $M = 0.46$, $SD = 0.78$, $t(49) = 2.66$, $p = .008$, Cohen's $d = .72$.

Did the Bipolar and Control Groups Differ in their Cardiovascular Threat Reactivity to the Evaluative Stressor?

Reactivity scores were computed by subtracting the mean level of cardiovascular threat reactivity during baseline from the mean level obtained during the 3-min stressor task. Because there were no significant main effects of task minute or significant group by minute interactions, we collapsed across task minutes to create a mean reactivity score for the stressor task. As predicted, there was a significant group difference on the cardiovascular threat reactivity index, $t(49) = 2.02$, $p = .044$, Cohen's $d = .58$, [1] with the bipolar group showing significantly greater increases in cardiovascular threat reactivity, $M = 0.52$, $SD = 1.95$, than did the control group, $M = -0.58$, $SD = 1.80$ (see Figure 1).

Confound Analyses

We considered the potentially confounding effects of subsyndromal depressive symptoms, comorbid anxiety disorder status, and psychotropic medications on emotional reactivity and physiological reactivity. In particular, within the bipolar group only, we computed zero-order correlations of BDI–SF scores; comorbid anxiety disorder status (presence vs. absence); and moodstabilizer, antidepressant, and lamotrigine dose equivalency scores with self-reported changes in anxiety and the cardiovascular threat reactivity index.

[1]Post hoc tests of group differences in the two components of the cardiovascular threat reactivity index revealed a marginal group difference in CO, $t(49) = 1.68$, $p = .094$, Cohen's $d = .46$, with the bipolar group showing greater decreases in CO, $M = -0.59$, $SD = 1.10$, than did the control group, $M = -0.08$, $SD = 1.10$, and a significant group difference in TPR, $t(49) = 2.16$, $p = .032$, Cohen's $d = .61$, with the bipolar group showing greater increases in TPR from baseline during the task, $M = 361.55$, $SD = 390.69$, than did controls, $M = 160.13$, 95, $SD = 250.89$.

Subsyndromal depressive symptoms were not significantly correlated with pretest changes in anxiety or with cardiovascular threat reactivity (all *r*s < |.29|, *p*s > .140). Comorbid anxiety disorder status was not significantly correlated with pretest changes in anxiety, $r = -.29$, $p = .146$, but was significantly correlated with cardiovascular threat reactivity, $r = -.39$, $p = .043$. None of the three classes of medication were significantly correlated cardiovascular threat reactivity, all *r*s < |.23|, all *p*s > .262. Mood stabilizers and lamotrigine were not significantly correlated with pretest changes in anxiety, *r*s < .28, *p*s > .167, but antidepressants were, $r = .55$, $p = .009$.

Discussion

Environmental stress is a robust predictor of the course of bipolar disorder, including episode duration, relapse, and symptom severity (Johnson, Cuellar, & Peckham, 2014). Although naturalistic studies suggest that bipolar disorder may be tied to greater stress reactivity, findings from laboratory-based studies have been mixed, and no prior study has examined autonomic physiological reactivity to an acute stressor in a sample of individuals diagnosed with bipolar I disorder. The present investigation sought to address this gap in the literature by examining emotional and cardiovascular reactivity to a goal-relevant stressor among individuals with this illness. In particular, individuals meeting diagnostic criteria for bipolar I disorder and a well-matched control group of individuals with no history of mood disorder were told their performance would be evaluated on a putative test of general intelligence—a core attribute that is widely valued across diverse domains and individuals (Crocker & Wolfe, 2001; Kirkpatrick & Ellis, 2001; Leary & Baumeister, 2000).

We hypothesized that compared to controls, individuals with bipolar disorder would show a pattern of exaggerated emotional and cardiovascular threat reactivity. Consistent with our predictions, participants in the bipolar group reported significantly greater increases in anxiety on receiving the task instructions and exhibited greater cardiovascular threat reactivity during task performance than did those in the control group. Whereas the normative cardiovascular response within the bipolar group was consistent with threat, the control group demonstrated an average cardiovascular response profile consistent with challenge.

Analyses also examined the role of comorbid anxiety and anti-depressant the profile of emotional and cardiovascular threat reactivity among individuals with bipolar disorder.

Past studies have found that as many as 60% of individuals diagnosed with bipolar disorder have at least one comorbid anxiety disorder, and more than 30% have multiple anxiety disorders (Bauer et al., 2005; Boylan et al., 2004; Mantere et al., 2006; Mitchell et al., 2013; Otto et al., 2006; Simon et al., 2004). In the present study, 37% of individuals in the bipolar group were found to have a comorbid anxiety disorder, and half had two or more anxiety disorders. Comorbid anxiety thus appears to be a central feature of bipolar disorder—the norm rather than the exception in this illness.

Further warranting attention, there is also robust evidence that comorbid anxiety is associated with a worse illness course and well-being. For example, anxiety has been

associated with an earlier age at onset of bipolar disorder (Simon et al., 2004); more frequent mood episode relapse (Boylan et al., 2004; Otto et al., 2006); greater illness chronicity and severity (Gaudiano & Miller, 2005); higher rates of substance abuse, sleep disturbance, and suicidality (Simon et al., 2004; Vieta et al., 2000); greater resistance to treatment (Boylan et al., 2004; Keller, 2006; Perlis et al., 2010); and reduced quality of life (Boylan et al., 2004).

The results of the present study suggest that diagnoses of anxiety are associated with greater cardiovascular threat reactivity to acute, goal-oriented stressors, adding to the list of complications conferred by this comorbidity. This finding has potentially important functional, health, and treatment implications. In terms of functioning, the cardiovascular threat response, which is characterized by decreased cardiac efficiency and increased vascular resistance, has been associated independently and conjointly with difficulty mobilizing cognitive resources toward optimal mental and physical performance (e.g., Eysenck, Derakshan, Santos, & Calvo, 2007; Jamieson, Nock, & Mendes, 2012; Kassam et al., 2009). The greater tendency of individuals with comorbid anxiety to engender this response could thus increase the likelihood of their experiencing disappointment or failure in the face of goal pursuit, thereby eroding personal morale. As a result, individuals with bipolar disorder and comorbid anxiety may be more vulnerable to disengaging their efforts from valued domains, or withdrawing from the pursuit of goals that are personally meaningful but nonetheless experienced as threatening (Major & O'Brien, 2005). Such behaviors would inadvertently stem opportunities for experiencing positive emotion and reward, which could otherwise help to quell persistent fears, bolster confidence, or repair a depressed mood (Kircanski, Joormann, & Gotlib, 2012), resulting in a vicious cycle of despondence.

From a long-term health perspective, bipolar disorder and anxiety have each been linked to an increased prevalence of cardiovascular disease (Kubzansky, Kawachi, Weiss, & Sparrow, 1998; Weiner, Warren, & Fiedorowicz, 2011), and the comorbidity of these two illnesses is likely to have additive or even synergistic effects. More work in this area is called for, given that acute cardiovascular responses to stress have been shown to relate to both chronic cardiovascular disease and cognitive dysfunction. One component of the cardiovascular threat response—increased vascular resistance—may contribute to hypertension if engendered repeatedly over time (Blascovich, Spencer, Quinn, & Steele, 2001); and indeed, one mechanism by which chronic anxiety has been proposed to increase cardiovascular disease risk is by promoting atherogenesis via increased hypertension (Kubzansky et al., 1998). The other component of the threat response— decreased cardiac output— has been associated cross-sectionally with executive dysfunction and accelerated brain aging in cardiac patients free of end-stage heart disease (Jefferson, Poppas, Paul, & Cohen, 2007; Jefferson, Tate, et al., 2007). Although longitudinal research is needed to more fully understand the mechanisms driving these associations, they are notable when considered alongside the robust evidence of cognitive deficits (Arts et al., 2008; Bora et al., 2009; Robinson et al., 2006) and elevated cardiovascular morbidity and mortality in bipolar disorder (Weiner, Warren, & Fiedorowicz, 2011b). Finally, although our findings and those of past studies point to the benefits of managing anxiety symptoms in bipolar disorder, this is often done pharmacologically through the use of antidepressant medications, which introduce the risk of drug-induced manic switch (Keller, 2006). In consequence, the need to

develop effective psychotherapeutic treatments that address bipolar disorder and comorbid anxiety is imperative. Encouragingly, at least one study of bipolar disorder has found that although individuals with comorbid anxiety had more severe illness characteristics, the magnitude of their treatment gains in cognitive– behavioral therapy and psychoeducation was equivalent or superior to that of participants without anxiety on a variety of outcome measures (Hawke, Vleyvis, & Parikh, 2007).

In regard to subjective anxiety, we found that individuals with bipolar disorder who reported greater increased pretest anxiety from baseline were also prescribed higher doses of antidepressant medication. It is likely that negative affectivity—a general underlying sensitivity to experiencing negative emotion—was driving both the use of antidepressants and the experience of heightened anxiety observed in anticipation of an acute stressor; however, our design was not ideally suited for disentangling this relationship and future research in this area is warranted.

This study has several strengths. First, to our knowledge it is the only laboratory investigation to assess acute stress reactivity using autonomic parameters in a sample of individuals diagnosed with bipolar I disorder. Second, drawing on the biopsychosocial theory of challenge and threat, this study goes beyond merely assessing arousal, or the magnitude of stress responses, to differentiate between adaptive and maladaptive stress typologies that may have important long-term physical and mental health implications. Third, we recruited a community-based sample of participants who were carefully diagnosed using a well-validated structured clinical interview. Finally, participants completed the study procedures during the interepisode period. Although residual symptoms in bipolar disorder are normative (Judd et al., 2002) and some of our participants did report mild mood symptoms during this interepisode period, the average symptom scores for mania and depression were well below clinical cutoffs, minimizing mood-state dependent effects on the findings.

Several limitations also are apparent. First, despite obtaining statistical support for our hypotheses, it is important to note that our sample size was small, and thus our findings require replication. Second, although the bipolar group exhibited worse performance on the stressor (i.e., complex working memory task) than did controls, a finding that is in line with much previous research, our methods preclude us from attributing this to the maladaptive pattern of emotional and cardiovascular threat responding that we observed. Still, it is notable that although both groups demonstrated comparable increases in general arousal while performing this task, as indexed by their relative changes in PEP from baseline, the control group showed an overall pattern consistent with challenge and the bipolar group showed an overall pattern consistent with threat. Third, we did not directly assess appraisals of challenge and threat in conjunction with the cardiovascular parameters; however, we did assess participants' reports of confidence and anxiety, which reflect subjective dimensions of challenge and threat, respectively (Blascovich & Mendes, 2000; Mendes et al., 2008; Skinner & Brewer, 2002). Indeed, the bipolar group reported greater increases in pretest anxiety on average and exhibited a convergent pattern of heightened cardiovascular threat reactivity. Finally, although previous literature has suggested that the threatrelated emotional and cardiovascular response profiles observed herein might have long-term repercussions

for executive functioning and cardiovascular health, we did not assess these relationships in the present study.

In sum, the present findings suggest that in the face of personally meaningful stressors, individuals with bipolar I disorder show exaggerated emotional and cardiovascular threat reactivity, both of which have been linked to a range of longer term deleterious health effects. Moreover, the exaggerated cardiovascular threat responding observed in the bipolar group was strongly coupled to the presence of comorbid anxiety, underscoring that comorbid anxiety is a major aspect of bipolar disorder that researchers and treatment providers would do well to address.

By taking a careful multimethod approach, including the use of an active, goal-relevant stressor, a fine-grained assessment of cardiovascular responses, and a close examination of the effects of depressive symptoms, comorbid anxiety, and psychotropic medication, our investigation yielded novel information regarding emotional and physiological responses to acute stress exposure and their associations with negative affectivity among individuals with bipolar disorder.

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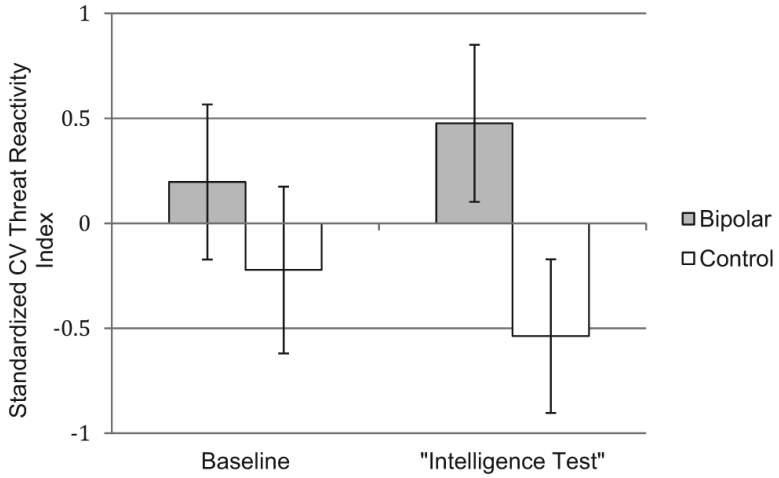

Figure 1.

Group differences in cardiovascular “threat” reactivity. CV = cardiovascular. Error bars represent ± standard error of the mean.

Table 1

Sample Characteristics

Characteristics	Bipolar (*n* = 27) *M* (*SD*)	Control (*n* = 24) *M* (*SD*)	Group difference
Age	35.63 (12.59)	30.42 (11.09)	$t(49) = 1.56$, $p = .119$
Gender (% female)	56	50	χ^2 (1) = 0.16, $p = .692$
BMI	26.39 (5.70)	23.87 (4.22)	$t(49) = 0.5\ 1$, $p = .067$
Manic symptom score (ASRM)	3.33 (2.73)	3.75 (3.15)	$t(49) = 0.26$, $p = .613$
Depressive symptom score (BDI)	4.70 (3.76)	0.83 (1.63)	$t(49) = 4.86$, $p < .001$
Age onset mania	20.7 (8.57)	—	—
Number lifetime manic episodes	5.08 (3.41)	—	—
Age onset depression	17.22 (9.05)	—	—
Number lifetime depressive Episodes	7.98 (8.22)	—	—
% with comorbid anxiety disorder	37	0	χ^2 (1) = 11.06, $p = .001$

Note. ASRM = Altman Self-Rating Mania scale; BDI = Beck Depression Inventory.