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Social Stress Response in Adolescents with Bipolar Disorder

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Abstract

Objective: Theoretical models posit that stressors contribute to the onset and maintenance of bipolar disorder in adolescence through disruptions in stress physiology, but physiological response to stressors has not been evaluated in adolescents with bipolar illness. The present study tests the hypothesis that adolescents with bipolar disorder will have greater reactivity to a laboratory social stress task than healthy adolescents.

Method: Adolescents with bipolar illness ($n=27$) and healthy adolescents ($n=28$) completed a modified version of the Trier Social Stress Task. Stress response was assessed using high frequency heart rate variability (HF-HRV), heart rate (HR), mean arterial blood pressure (MAP), salivary cortisol, and subjective stress. Multilevel models were used to test for group differences in resting-state physiology, and stress reactivity and recovery.

Results: Adolescents with bipolar disorder had greater reactivity in HF-HRV ($z = 3.32$), but blunted reactivity in MAP ($z = -3.08$) and cortisol ($z = -2.60$), during the stressor compared to healthy adolescents. They also had lower resting HF-HRV ($z = -3.49$) and cortisol ($z = -2.86$), and higher resting HR ($z = 3.56$), than healthy adolescents.

Conclusions: These results indicate that bipolar disorder is associated with disruptions in autonomic and endocrine response to stress during adolescence, including greater HF-HRV reactivity. Further research should evaluate whether these individual differences in stress physiology precede and predict the onset of mood episodes.

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Keywords

bipolar; adolescence; stress; psychophysiology; heart rate variability

1. Introduction

Bipolar disorder, which is characterized by dramatic and alternating episodes of elevated and depressed mood, typically begins in late adolescence or early adulthood (Kessler et al., 2005) and includes recurrent or subsyndromal mood episodes across the lifespan (Birmaher et al., 2009). The early age of onset and consequent distress and dysfunction related to bipolar illness make it a leading cause of psychiatric disability (World Health Organization, 2008). Bipolar disorder is also associated with an alarmingly high risk for suicide (Angst et al., 2002), and adolescents with bipolar disorder are especially vulnerable (Goldstein et al., 2010). The high degree of functional impairment and risk associated with bipolar illness are compelling reasons to identify and understand its predisposing and perpetuating factors.

While bipolar disorder is highly heritable, environmental factors account for approximately 40% of disorder incidence (Lichtenstein et al., 2009) and psychosocial stressors moderate genetic risk (O'Connell, 1986). High rates of stressors are common during the months before the onset of mood episodes in bipolar disorder (Johnson et al., 2016; Lex et al., 2017), and heightened or disrupted reactivity in neuroendocrine stress response systems may increase risk for episode onset and maintenance (Johnson, 2005). The combined effects of exogenous stress exposure and endogenous stress reactivity may create a “perfect storm” for the onset of bipolar illness in vulnerable adolescents, particularly given that adolescents report more stressful life events than children (Ge et al., 1994; Larson and Ham, 1993) and are more reactive to stressors than adults (Romeo, 2010).

Existing research on stress response in bipolar disorder has focused on adults and provides mixed evidence of disruptions in stress reactivity. Some studies indicate that adults with bipolar disorder have different affective (Myin-Germeys et al., 2003), cognitive (Ruggero and Johnson, 2006), and physiological (Depue et al., 1985; Muhtadie and Johnson, 2015; Wieck et al., 2013) responses to real-world and laboratory stressors than healthy adults. However, most results indicate that healthy adults and those with bipolar disorder have comparable affective responses to stressors (Cuellar et al., 2009; Edge et al., 2015; Havermans et al., 2010; Ruggero and Johnson, 2006). Furthermore, while two studies found that adults with bipolar-spectrum disorders have increased cortisol reactivity (Depue et al., 1985) and cardiovascular threat reactivity (Muhtadie and Johnson, 2015) compared to healthy controls, other studies report that healthy adults and adults with bipolar disorder have comparable stress-related increases in heart rate (Edge et al., 2015) and cortisol (Havermans et al., 2011; Steen et al., 2011), and one found that euthymic women with bipolar disorder had blunted heart rate and cortisol reactivity to a social stress task relative to healthy women (Wieck et al., 2013). The scarcity of research on stress reactivity in bipolar disorder and the variability in existing study results underscore the need for comprehensive assessment of stress response systems (e.g., autonomic, endocrine, affective) and their potential moderators (e.g., age, sex, body mass index, medication load, symptom severity).

In addition, research on stress reactivity at different stages of neurodevelopment and disease progression is needed to identify developmentally relevant risk factors for mood disorders and determine whether disruptions in stress reactivity are a cause or a consequence of bipolar illness.

The present research evaluates physiological and affective measures of reactivity to social stress in a sample of adolescents with bipolar illness relative to psychologically healthy adolescents. Stress reactivity was assessed using five different indices: high frequency heart rate variability (HF-HRV), heart rate (HR), mean arterial blood pressure (MAP), salivary cortisol, and subjective stress. HF-HRV reflects parasympathetic nervous system activity, where higher tonic HF-HRV reflects greater vagal inhibition of sympathetic activity, and decreases in HF-HRV during social stress are associated with social disengagement, emotion dysregulation, and increased risk for psychopathology (Beauchaine and Thayer, 2015; Porges, 2001; Thayer and Sternberg, 2006). HR and MAP are common measures of autonomic function, where higher tonic HR and MAP reflect autonomic arousal, and stress-related increases in HR and MAP reflect vagal withdrawal and sympathetic mobilization. Cortisol provided an index of hypothalamic-pituitary-adrenal (HPA) response, where basal cortisol levels and cortisol reactivity are both associated with exposure to stressors and psychopathology (Heim and Nemeroff, 2001; Lopez-Duran et al., 2009; Zorn et al., 2017), but their directions of association are moderated by characteristics of the sample (e.g., age, gender, psychopathology) and the stressors (e.g., severity, chronicity, timing; Booij et al., 2013; Bosch et al., 2009; Elzinga et al., 2008; Kuhlman et al., 2015a; Kuhlman et al., 2015b; Laceulle et al., 2017).

Based on a theoretical model in which increased stress sensitivity and/or decreased stress regulation, particularly in the context of social stressors, contributes vulnerability to mood disruption in adolescents, we tested the hypothesis that adolescents with bipolar illness, relative to controls, would have greater stress-related decreases in HF-HRV, and increases in HR, MAP, and subjective stress, compared to healthy adolescents. We also expected cortisol response to social stress to differ between adolescents with bipolar illness and healthy controls, but we did not hypothesize a specific direction of association because existing literature is inconsistent. In addition, based on evidence that adults with bipolar disorder have lower resting HF-HRV than healthy adults (Faurholt-Jepsen et al., 2017) and more hypertension than adults without a mood disorder (Goldstein et al., 2009), we also predicted that adolescents with bipolar disorder would have lower resting HF-HRV, and higher resting MAP, than healthy adolescents. Finally, we also conducted exploratory analyses to evaluate potential moderators of stress response in bipolar and healthy adolescents, including age, sex, body mass index, medication load, and the severity of current mood symptoms.

2. Method

2.1. Participants

Participants were 27 adolescents with bipolar disorder and 28 healthy adolescents who enrolled in a study on sleep, stress response, and brain function at the University of Pittsburgh. Participants with bipolar disorder were recruited from a specialty mood disorders clinic after being diagnosed with bipolar type I ($n=9$), II ($n=9$), or not otherwise specified

(NOS; $n=9$) using validated procedures (Axelson et al., 2011). All bipolar subtypes were included because they are associated with similar degrees of functional impairment and have high rates of subtype-conversion over follow-up (Birmaher et al., 2009). Healthy participants were recruited from the community using internet and paper advertisements. The inclusion criteria for both groups were: 1) current age 13 years, 0 months to 22 years, 11 months; 2) English language fluency and at minimum a 3rd grade literacy level; and 3) ability and willingness for the adolescent and their parent or legal guardian (for participants under 18 years of age) to provide informed consent/assent to participate. The exclusion criteria were: 1) evidence of intellectual disability, pervasive developmental disorder, or organic central nervous system disorder (e.g., epilepsy) identified through medical record review or diagnostic interview; 2) a life-threatening medical condition requiring immediate treatment; or 3) past participation in other studies with similar tasks, or a sibling enrolled in the study (to preserve task credibility). Additional exclusion criteria for participants with bipolar disorder were: 1) psychiatric symptom severity requiring hospitalization; or 2) apnea-hypopnea index of ≥ 15 events/hr of sleep assessed via ApneaLink (ResMed, San Diego, CA). Additional exclusion criteria for healthy participants were: 1) past mood or anxiety disorder, or any current psychiatric diagnosis; 2) first-degree relative with history of bipolar disorder; 3) sleep disorder or other major medical problem, including apnea-hypopnea index of ≥ 15 events/hr of sleep; 4) currently taking medications known to affect sleep/wake function, or 5) fMRI contraindications. Contraindications for sleep disorders other than apnea, medications that affect sleep-wake function (e.g., hypnotics, psychotropics), and fMRI were not exclusion criteria for adolescents with bipolar disorder due to recruitment feasibility. All recruitment and laboratory procedures were approved by the university's Institutional Review Board.

2.2. Clinical Assessments

Clinical assessments were completed after obtaining informed consent/assent, and 1–3 weeks before the stress protocol (described below). The Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime (K-SADS; Kaufman et al., 1997) was used to diagnose current and past psychiatric disorders based on criteria in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; American Psychiatric Association, 2000). Out of 13 tapes reviewed for inter-rater reliability (23.6%), kappas were high for diagnosis of bipolar disorder (0.90), distinguishing subtypes of bipolar disorder (0.79), and diagnosis of disorders other than mood disorders (0.80). The Longitudinal Interval Follow-Up Evaluation (LIFE; Keller et al., 1987) was used to rate the severity of depressive, manic, and hypomanic episodes for the 12 weeks up to and including the clinical assessment visit. A locally-developed Structured Clinical Interview for Sleep Disorders, along with ApneaLink assessment, was used to diagnose current sleep disorders. The Mood and Feelings Questionnaire–Child Version (MFQ; Angold et al., 1995) was used to index the severity of depressive symptoms. MFQ scores above 28 have high sensitivity and specificity for identifying youth with a current major depressive episode (Daviss et al., 2006). Height and weight were measured in duplicate and mean values were used to calculate body mass index (BMI).

Medical record review and participant report were used to record psychiatric medications and dosing that were current at the initial study visit. Medications were given one of six classifications – antidepressant, antipsychotic, anxiolytic, mood stabilizer, sedative/hypnotic, or stimulant – and the dose of each medication was coded on a 3-point scale: absent (0), low (1), or high (2; Phillips et al., 2008). For antipsychotics, low/high dosages were compared to the mean effective daily dose based on chlorpromazine equivalents for antipsychotics (Davis and Chen, 2004), and for other medications, referenced to the midpoint of the recommended daily range in the *Physician's Desk Reference* (Invanz, 2017). The ratings for each medication were summed to represent the overall medication load within each medication class.

2.3. Procedure

Participants began the standardized stress protocol in the late afternoon (between 4:30 pm and 8:00 pm) to control for diurnal patterns in physiological outcomes. Eligible participants underwent a 1 h functional magnetic resonance imaging (fMRI) scan, and all participants completed a 1 h pupillography session, prior to beginning the stress protocol. Participants completed a modified version of the Trier Social Stress Task (TSST; Kirschbaum et al., 1993). The TSST is a laboratory-based social-evaluative threat task that reliably elicits subjective stress and an increase in the stress-hormone cortisol (Dickerson and Kemeny, 2004). The standard TSST includes preparation to give a speech (10 min), followed by delivery of the speech (5 min) and a serial subtraction task (5 min) in front of a video recorder and a panel of two impassive judges who are introduced as experts in public speaking. The task was modified in the current study to include 6 min each for speech preparation, speech delivery, and serial subtraction; the speech and serial subtraction tasks were performed in front of a large video camera on a tripod and two individuals – the research assistant and a judge who was described as an expert in non-verbal behavior; and participants were asked to make a speech as if defending themselves in court regarding shoplifting charges while being as persuasive as possible (Franzen et al., 2011; Marsland et al., 1995). The social stress task (SST) was preceded by a 20 min pre-stress baseline period, and followed by a 60 min recovery period. Participants remained seated in the same room during the baseline, stress, and recovery periods. A novel SST environment was created by the introduction of a video camera during speech preparation, video recording and the presence of an unfamiliar judge during the speech delivery and serial subtraction tasks, and the presentation of a nature video during the baseline and recovery periods.

Stress was measured through physiological and subjective measures during the baseline, SST, and recovery periods. Electrocardiography was performed continuously at 1024 Hz using Grass amplifiers and Harmonie collection software. Data files were imported into MindWare HRV 3.0 (Gahanna, OH) for processing the HR outcomes. Autoregressive spectral analyses of the interbeat interval were used to derive 2 min averages of heart rate (HR; 49 samples total; 10 samples during baseline, 9 samples during the SST, 30 samples during recovery). Heart rate variability within the high frequency range (0.15-0.40 Hz; HF-HRV), indexing activity in the parasympathetic nervous system, was calculated using absolute power from spectral analyses. Blood pressure was recorded every 2 min for the final 10 min of the baseline period (5 samples), during the SST beginning at 1 min after the

start of speech preparation (9 samples), and during the first and last 10 min of the recovery period (5 samples each; 27 samples total) using a Critikon Dinamap 8100 monitor to determine the mean arterial pressure (MAP) via oscillometric method. The abbreviated sampling periods for blood pressure minimized participant discomfort related to cuff inflation. Saliva samples were collected at the end of the pre-stress baseline, immediately following the SST, and at minute 20, 40, and 60 during the recovery period (5 samples total) using Sarstedt Salivettes (Niimbrecht, Germany). Salivettes were frozen at -80°C until radioimmunoassay for cortisol using commercial kits from ALPCO Diagnostics (Salem, NH). Subjective stress was assessed on an 11-point Likert scale (0, low; 10 high) at the end of the pre-stress baseline, SST, and recovery periods (3 samples).

2.4. Analytic Approach

First, descriptive statistics were used to evaluate the extent of missing data and the distribution of the data (e.g., normality, equality of variance, outliers). Participants with fewer than 50% useable samples for any given measure were omitted from analyses for that measure (1 participant for MAP, 3 participants for HR). One participant halted the SST, resulting in missing recovery data for HR. This participant was included in analyses for the resting baseline and SST periods because they had $> 50\%$ useable samples. Natural log transformation was applied to HF-HRV to better approximate a normal distribution.

Second, mean plots and model fit were evaluated to identify discontinuities in each outcome over time (e.g., at the initiation of the SST) and determine whether estimates of change in each outcome followed a linear or quadratic course. Mean plots for HF-HRV, HR, and MAP at each time point indicated that, as anticipated, there was negligible systematic change over time during the resting baseline period, followed by quadratic change in outcomes after the initiation of the SST, and relatively linear change in outcomes during recovery (see Figure 1). As a result, separate multilevel models were performed for the resting baseline, SST, and recovery periods. Chi-square difference tests were used to evaluate fit for models with linear versus linear and quadratic slopes, separately for the SST and recovery periods. Model fit was significantly improved when random quadratic effects were estimated for the SST ($ps < .05$), but not recovery ($ps > .05$); as a result, both linear and quadratic slopes were estimated for the SST and a more parsimonious linear model was estimated for the recovery period. HF-HRV, HR, and MAP recovered to baseline levels within 10 min of the SST; therefore, models for the recovery period included the first five, 2 min samples.

Third, multilevel models (for HF-HRV, HR, MAP, and cortisol) and repeated-measures ANOVA (for subjective stress) were used to evaluate whether adolescents with bipolar illness: 1) differ from healthy controls in resting-state HF-HRV, HR, MAP, cortisol, and subjective stress; 2) have greater reactivity to the SST than healthy controls; and 3) have slower recovery from the SST than healthy controls. Excepting analyses with cortisol, separate multilevel models were run for the baseline (2-20 min of recording), SST (22-38 min of recording), and recovery periods (40-48 min of recording). Analyses of cortisol response included all five samples (one at the end of the baseline period, one immediately after the SST, and three during recovery) in a single model. All multilevel models used robust maximum likelihood (MLR) estimation and were performed in MPlus-7 (Muthén and

Muthén, 1998-2017). Time was included as a first-level predictor after scaling it to equal minutes divided by the sampling frequency (2 min for HF-HRV, HR, and MAP; 20 min for cortisol) and centering it at the initial value for each period of analysis (min 2 for baseline, min 22 for SST, and min 40 for recovery of HF-HRV and HR; min 12 for baseline, min 22 for SST, and min 40 for recovery of MAP; min 20 for cortisol). Group was included as a second-level predictor of the intercept, linear slope (for baseline, SST and recovery), and quadratic slope (for SST). Repeated-measures ANOVA was used to evaluate group differences in subjective stress response. ANOVAs were performed in SPSS-23 (IBM Corporation, 2015). Multilevel models were not used to estimate change in subjective stress over time because a quadratic model would be under-identified to test random effects with three samples per participant.

Fourth, exploratory analyses were performed to evaluate whether participants' age, sex, BMI, and participation in the MRI scan predicted HF-HRV, HR, MAP, cortisol, or subjective stress during the SST. Variables that accounted for a significant portion of the variance in outcomes were included in sensitivity analyses for the primary hypothesis tests. Multilevel models used MLR estimation with Time as a first-level predictor of each outcome. Age, Sex, BMI, and Scan were included as second-level predictors of the intercept (the first sample of the SST) and the linear and quadratic slopes. Age and BMI were centered on the grand mean. Repeated measures ANOVA was used to test the effect of Time (three samples) and Age, Sex, BMI, and Scan on subjective stress response.

Fifth, we performed exploratory analyses to evaluate whether medication load would predict stress response in adolescents with bipolar disorder. The load for the three most common classes of medication in the bipolar sample (prescribed in at least 40% of cases; antipsychotics, mood stabilizers, and stimulants) were included as three second-level predictors in multilevel models of SST response with Time as a first-level predictor. Medication load was not added to models comparing participant groups because psychiatric medication use was dependent on group-membership (i.e., none of the healthy participants had a current prescription for psychiatric medications).

Finally, given the high frequency and duration of subsyndromal symptoms during interepisode periods (Birmaher et al., 2009), multilevel models were performed to evaluate whether depression severity in adolescents with bipolar disorder was associated with: 1) resting-state HF-HRV, HR, MAP, and cortisol; 2) reactivity to the SST; and 3) recovery from the SST. Consistent with tests of group differences, models used MLR estimation with Time as a first-level predictor. Depression severity was included as a second-level predictor of the intercept, linear slope (for baseline, SST and recovery), and quadratic slope (for SST). Identical models were also completed in the full sample, with MFQ scores as a second-level predictor instead of Group, to supplement planned group comparisons. Mania symptom severity was not similarly examined due to the absence of symptoms meeting DSM-IV criteria for a manic episode, and the relatively limited number of participants with subthreshold manic symptoms.

3. Results

3.1. Descriptive Characteristics

The control and bipolar groups had comparable distributions for Sex, Age, and Race ($ps > .05$), while BMI was higher (overweight) in the bipolar group ($p < .05$); see Table 1. Eight participants with bipolar disorder did not participate in the MRI scan prior to the SST. As anticipated, there was a significant group difference in self-reported depression severity on the MFQ in which adolescents with bipolar disorder had greater depressive symptom severity than healthy adolescents, $t(53) = -4.40$, $p < .001$; see Table 1. Based on LIFE ratings at the baseline assessment, mood symptom severity varied within the participants with bipolar disorder: 12 were euthymic, 7 had subsyndromal depression, 3 had subsyndromal hypomania, 3 had subsyndromal mixed symptoms (i.e., both subsyndromal depression and hypomania), 1 had syndromal hypomania, and 1 had syndromal depression. The average age of onset of manic or hypomanic symptoms that impaired functioning was 11 years ($SD = 3.90$). Most patients (70%) had current comorbid mental disorders (11 attention deficit hyperactivity, 8 anxiety, 4 conduct/oppositional-defiant, 4 sleep/circadian, 2 substance, 2 other). Furthermore, all 27 patients were prescribed at least one psychiatric medication: 18 mood stabilizers, 17 antipsychotics, 11 stimulants, 7 antidepressants, 3 anxiolytics, and 1 sedative/hypnotic. The average load for the three most common classes of medication was 1.83 for mood stabilizers, 2.35 for antipsychotics, and 1.55 for stimulants.

3.2. Differences between Adolescents with Bipolar Disorder and Healthy Adolescents

3.2.1. Resting state.—Multilevel models for the resting baseline period indicated that there were group differences in initial levels of HF-HRV and HR, but not MAP; see Table 2 and Figure 1. At the start of the baseline period, adolescents with bipolar disorder had lower HF-HRV (lower y-intercept) and higher HR (higher y-intercept) than healthy adolescents. There was also a significant main effect of Time on MAP, but not HF-HRV or HR, during the baseline period. MAP decreased linearly during the baseline period in both groups (negative slopes). The results for cortisol and subjective stress are reported in the next section because responses from baseline through recovery were estimated in a single model.

3.2.2. Stress reactivity.—Multilevel models for the SST indicated that there were group differences in initial levels of HF-HRV, HR, and cortisol; see Table 2 and Figure 1. At the start of the SST, adolescents with bipolar illness continued to have lower HF-HRV and higher HR than healthy controls. Adolescents with bipolar illness also had lower cortisol levels than controls at the start of the SST.

There were also significant interaction effects of Group x Time on HF-HRV, HR, and cortisol during the SST; see Table 2 and Figure 1. Model estimates of linear and quadratic change indicated that adolescents with bipolar disorder had more reactivity in HF-HRV (greater linear and quadratic slopes during the SST), and blunted MAP and cortisol reactivity (diminished linear and quadratic change), relative to healthy controls. There were not significant group differences in linear or quadratic change in HR during the SST.

Repeated measures ANOVA indicated that there were not group differences in subjective stress reactivity; Time x Group $F(2,52) = 1.30, p > .05$. Both groups had equivalent increases in subjective stress during the SST; Time $F(2,52) = 89.95, p < .001$; Mean(SD) = 0.81(2.08) during baseline, 5.85(2.80) during SST, and 0.87(2.28) during recovery.

3.2.3. Stress recovery.—Estimates of the intercept and linear change in stress outcomes during the recovery period indicated that there were group differences in initial levels of HF-HRV and HR; see Table 2. At the start of the recovery period, adolescents with bipolar disorder continued to have lower HF-HRV and higher HR than healthy controls (significant effects of group on y-intercepts). There were no significant group effects on linear change in HF-HRV, HR, or MAP during the recovery period.

3.3. Sensitivity Analyses

Multilevel models and repeated measures ANOVA indicated that Sex, Age, and Scan did not significantly affect HF-HRV, HR, MAP, cortisol, or subjective stress during the SST with the following exception: there was a significant effect of Sex on HR at the start of the SST where females had higher HR than males; see Table A.1. Subsequent multilevel models with Group, Sex, and their interaction as predictors did not result in a significant interaction of Sex x Group on HF-HRV, HR, MAP, or cortisol during the SST ($ps > .05$ for the intercept and linear and quadratic slopes). In consequence, Sex, Age, and Scan were omitted from subsequent analyses to maximize model parsimony. Multilevel models indicated that BMI predicted HF-HRV, HR, MAP, and cortisol during the SST; see Table A.1. As a result, BMI was included as a covariate in sensitivity analyses. Results from hypothesis tests that included BMI were comparable to those without the covariate; see Table A.2.

3.4. Exploratory Analyses in Adolescents with Bipolar Disorder

The results from exploratory models to evaluate associations between medication load and SST reactivity in adolescents with bipolar disorder are presented in Table 3. Higher doses of antipsychotics and stimulants were associated with greater reactivity in HF-HRV during the SST (greater linear and quadratic slopes). Higher doses of antipsychotics and stimulants were also associated with lower HF-HRV at the start of the SST (lower intercepts), and greater stimulant doses were associated with higher HR at the start of the SST (higher intercept). Physiological stress indices were not associated with the load of mood stabilizers. In addition, repeated measures ANCOVA indicated that subjective stress in adolescents with bipolar disorder was not predicted by the dose of antipsychotics [Time x Load $F(2,44) = 0.31, p > .05$], mood stabilizers [Time x Load $F(2,44) = 1.30, p > .05$], or stimulants [Time x Load $F(2,44) = 1.86, p > .05$].

The results from exploratory models to evaluate whether depressive symptom severity was associated with SST reactivity and recovery in adolescents with bipolar disorder are presented in Table 4. Higher levels of depressive symptoms were associated with lower HF-HRV at the start of recovery in adolescents with bipolar disorder. Depressive symptom severity was not significantly associated with HR, MAP, or cortisol response to the SST. Finally, repeated measures ANCOVA indicated that higher depressive symptom severity was associated with larger increases in subjective stress during the SST [Time x MFQ $F(2,46) =$

3.58, $p < .05$]. Supplemental multilevel models with the full study sample, using MFQ score instead of Group as a second-level predictor, paralleled the results of group comparisons for HF-HRV, HR, and cortisol; see Table A.3.

4. Discussion

We hypothesized that adolescents with bipolar illness would have greater reactivity to a laboratory social stress task than healthy adolescents, and we tested this hypothesis using five different indices: HF-HRV, HR, MAP, cortisol, and subjective stress. Our results provide initial evidence that adolescents with bipolar illness have more parasympathetic withdrawal (greater decreases in HF-HRV) during social stress compared to healthy adolescents. Greater parasympathetic withdrawal during social stress was not accompanied by greater sympathetic and endocrine mobilization. Rather, adolescents with bipolar disorder had “healthy” stress-related increases in HR, while MAP and cortisol response to social stress were both blunted relative to healthy adolescents. Parasympathetic withdrawal without sympathetic and endocrine mobilization suggests that bipolar disorder in adolescents is associated with inhibited vagal regulation of emotional response, as well as failure to engage sympathetic and endocrine systems that support “fight or flight” (Beauchaine, 2001; Porges, 2001). More broadly, group differences in HF-HRV, MAP, and cortisol reactivity indicate that, even at an early stage of development and bipolar progression, there is taxation across physiological systems that support social and behavioral function. Taxation in these stress response systems may be a consequence of genetic and environmental risk factors for bipolar illness, bipolar symptoms such as depressed mood, and/or antipsychotic and stimulant use (which paralleled the effects of Group on HF-HRV reactivity).

4.1 Comparison with Previous Research

Though this is the first study to evaluate HF-HRV reactivity in adolescents with bipolar disorder, blunted vagal reactivity is reliably associated with depression in adults (Hamilton and Alloy, 2016). Notably, associations between HF-HRV reactivity and depression may depend on resting vagal tone, where low vagal reactivity is associated with depressive symptoms in adults when resting vagal tone is also high (Yaroslavsky et al., 2013a; Yaroslavsky et al., 2013b). The amplified HF-HRV reactivity that we observed in adolescents with bipolar disorder was coupled with low resting HF-HRV, and low resting HF-HRV is often, though not reliably, observed in adults with bipolar disorder (Faurholt-Jepsen et al., 2017). In addition, both high and low parasympathetic tone have been associated with depressive disorder and depression symptom severity in children and adolescents (Hamilton and Alloy, 2016). Amplified vagal reactivity and low tonic vagal tone may both reflect impairment in the capacity of the central autonomic network to flexibly modulate sympathetic response (Thayer and Lane, 2000).

Adolescents with bipolar disorder had less MAP reactivity than controls, though hypertension is twice as prevalent in adults with bipolar disorder compared to adults without bipolar disorder (Goldstein et al., 2009), and elevated diastolic blood pressure has been observed in adolescents with bipolar disorder (Naiberg et al., 2016). Many studies do not screen for sleep apnea, as we did in this study, though sleep disordered breathing is common

in bipolar disorder (Sharafkhaneh et al., 2005; Soreca et al., 2012) and associated with poor metabolic health (Nieto et al., 2000). Vascular health may also be less impaired at early stages of bipolar illness (Murray et al., 2012). Low MAP reactivity in this sample could reflect decreased perfusion or increased vascular resistance during social stress. Notably, HR was higher in adolescents with bipolar disorder compared to healthy controls from baseline through recovery, and showed similar increases in both groups during the SST. This indicates that lower MAP reactivity in adolescents with bipolar disorder was not due to group differences in HR reactivity.

Adolescents with bipolar disorder also had lower cortisol reactivity during the SST compared to healthy adolescents. Low cortisol reactivity was also reported by Wieck et al. (2013), who compared SST response in euthymic women with bipolar disorder to response in healthy women. However, cortisol response to stressors did not show impairment in two other studies of bipolar adults (Havermans et al., 2011; Steen et al., 2011), and one study found increased cortisol reactivity in adults with cyclothymia compared to controls (Depue et al., 1985). We also observed low resting cortisol levels in adolescents with bipolar disorder, in contrast to a recent meta-analysis that reported high resting cortisol levels in adults with bipolar disorder (Belvederi Murri et al., 2016). In addition, resting cortisol was not related to depressive symptom severity in our sample of adolescents, though it has been associated with depression severity in older adults with bipolar disorder (Maripuu et al., 2014). Further research may be needed to identify moderators of tonic and phasic cortisol response in bipolar disorder, including illness state and duration, symptom severity, and developmental stage.

Consistent with studies in adults (Cuellar et al., 2009; Edge et al., 2015; Havermans et al., 2010; Ruggero and Johnson, 2006), we did not observe group differences in subjective stress during the SST; healthy and bipolar adolescents both reported increased stress during the SST relative to rest and recovery, but bipolar illness did not amplify subjective reports of stress. Furthermore, physiological stress reactivity was not associated with the severity of depressive symptoms. These results suggest that disruptions in sympathetic and endocrine stress physiology may be independent of state-level indicators of affect and depressive symptom severity.

4.2. Medication Load, Age, and Sex

Exploratory analyses to evaluate whether medication load would moderate physiological stress reactivity in adolescents with bipolar illness provided insights that may aid future research. The significant associations that we observed between cardiac physiology (HF-HRV, HR) and the dose of antipsychotic and stimulant medications in this sample could indicate that pharmacological treatment of bipolar illness, in combination with the illness itself, contributes to disruption in autonomic stress response systems. This interpretation is consistent with a meta-analysis on the effects of psychotropic medications on autonomic function, which found lower heart rate variability in patients with mood disorders relative to healthy controls, and larger group differences in patients using antipsychotic and antidepressant medications relative to unmedicated patients (Alvares et al., 2016). Psychotropic medications could also be an indicator of greater illness severity (e.g., the need

for antipsychotics for symptom management). Ideally, we would be able to dissociate the effects of bipolar illness and medication load. However, all of the adolescents with bipolar disorder in this study were prescribed one or more psychiatric medications, and it is not meaningful to try to “control” for medication use in analyses comparing healthy to bipolar adolescents when there are real group differences (Miller and Chapman, 2001). Our results may only generalize to adolescents in psychiatric treatment, although this is very common for individuals with bipolar disorder. Evaluating stress reactivity in unmedicated samples would help delineate the effects of medication load from bipolar illness, although such studies may be impractical given the wide use of psychotropics in patients with bipolar disorder.

Exploratory analyses to evaluate the effects of age and sex in the full study sample were largely non-significant. Girls had higher HR than boys during the SST, but neither age nor sex moderated the effects of group on HR or the other physiological outcomes. Given the association between low HF-HRV and decreased cognitive and emotional control (Thayer and Lane, 2000), we anticipated that low HF-HRV may also be associated with young age. Furthermore, because social stress is more salient for females than males (Rudolph, 2002), we anticipated that girls in this sample might have greater stress reactivity than boys. However, recent meta-analyses indicate that neither age nor sex moderate associations between bipolar disorder and tonic HF-HRV in adults (Faurholt-Jepsen et al., 2017), and older age but not sex is associated with higher basal cortisol in adults with bipolar disorder compared to controls (Belvederi Murri et al., 2016). Notably, associations between age and stress reactivity may not be apparent within the limited age range of this study sample (Kudielka et al., 2004a, b), and sex differences in autonomic and HPA reactivity to social stress appear to emerge during adolescence and early adulthood (Ordaz and Luna, 2012). Sex differences are also related to gonadal hormones (Ordaz and Luna, 2012), and may not be apparent in this study because we did not assess or control for menstrual phase, contraceptive use, or pubertal timing.

4.3 Strengths and Limitations

This study makes a number of important contributions to existing literature. Previous research on stress reactivity in bipolar disorder has been limited to adult samples and a few domains of stress response (e.g., self-reported affect, HR). This is the first study to characterize physiological response to social stress in adolescents with bipolar disorder. To our knowledge, it is also the first study to describe resting-state stress physiology in adolescents with bipolar disorder. Studying the correlates of bipolar disorder during adolescence is a key step in identifying potential mechanisms of disorder onset and symptom maintenance while neuroautonomic and endocrine systems that sustain health continue to develop. This study also evaluates stress response across multiple domains, including the autonomic nervous system, HPA axis, and subjective report. These systems do not act in isolation, and domain-specific responses (e.g., disruptions in HF-HRV reactivity but not HR reactivity) can help pinpoint specific mechanisms of disruption (e.g., parasympathetic response).

There are also significant limitations to this study, including the cross-sectional study design, absence of an unmedicated group of adolescents with bipolar disorder, sample size, and negligible cortisol response in controls. Unfortunately, this study cannot determine whether greater reactivity in HF-HRV is a cause or a consequence of bipolar illness. Furthermore, because all participants with bipolar disorder were prescribed psychiatric medications, group differences in stress physiology may be a consequence of treatment. Future research can address these limitations using prospective longitudinal assessment of stress physiology through adolescence and early adulthood in high-risk samples (e.g., offspring of parents with bipolar disorder). In addition, though the sample size in this study is consistent with many other studies on stress physiology in bipolar adults (Faurholt-Jepsen et al., 2017), the results of existing research are varied. Small sample sizes increase risk for sampling bias and spurious findings. Finally, the absence of a significant increase in cortisol among controls was surprising given previous research with similar paradigms (Dickerson and Kemeny, 2004). Cortisol reactivity may have been blunted in this study because the SST was completed after fMRI and pupillography tasks, and the SST was modified to include a single unfamiliar judge instead of two judges. However, the SST elicited significant responses in HF-HRV, MAP, and subjective stress, providing support for the validity of the stress manipulation.

4.4. Implications

Identifying the physiological and affective correlates of bipolar disorder in adolescence can provide clues about the predisposing and perpetuating factors for mood disturbance at this critical period of neurodevelopment. Disruptions in stress response may be especially relevant during adolescence, as self-regulation skills continue to develop and reactivity to social stress is heightened (Blakemore and Mills, 2014; Crone and Dahl, 2012). If stress reactivity contributes to the onset and maintenance of bipolar disorder during adolescence, interventions that boost resilience in the face of adversity could be key targets for intervention. Further research on stress reactivity in adolescents with bipolar disorder, and parasympathetic response in particular, should try to determine whether stress sensitivity is a mechanism of bipolar illness during adolescence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Bipolar adolescents exhibit disruptions in stress physiology compared to controls.
- Parasympathetic withdrawal during stress was heightened in bipolar adolescents.
- Cortisol response to social stress was blunted in bipolar adolescents.
- Antipsychotic and stimulant load also predicted parasympathetic withdrawal.
- Depression severity did not predict stress physiology in bipolar adolescents.

Figure 1. Mean (SE) physiological response in adolescents with bipolar disorder (grey line) and healthy adolescents (black line) during pre-stress baseline (0-20 min), social stress (22-38 min), and post-stress recovery (>38 min).

Table 1

Descriptive characteristics of the sample

Characteristic	Control (<i>n</i> = 28)	Bipolar (<i>n</i> = 27)
Sex, <i>n</i>	18 female	17 female
Race, <i>n</i>	4 Asian, 7 Black, 17 White	6 Black, 21 White
Age, <i>M</i> (<i>SD</i>)	19.19 (2.89)	18.22 (2.69)
BMI, <i>M</i> (<i>SD</i>)	24.40 (5.18)	28.15 (6.84) *
MFQ, <i>M</i> (<i>SD</i>)	4.04 (4.76)	17.23 (18.48) ***

Note. BMI, body mass index; MFQ, Mood and Feelings Questionnaire. One participant with bipolar disorder did not complete the MFQ (*n* = 26) and four participants with bipolar disorder did not complete BMI measurements (*n* = 23).

*
p < .05

p < .001.

Table 2

Group differences in physiological response during pre-stress baseline, social stress (SST), and post-stress recovery in adolescents with bipolar disorder and healthy controls.

Outcome	Control Z	Control <i>b</i>	Control SE	Bipolar Z	Bipolar <i>b</i>	Bipolar SE
HF-HRV						
Baseline (<i>n</i> = 52)						
Intercept	39.03***	6.61	0.17	-3.40***	-1.19	0.35
Linear Slope	0.08	0.00	0.01	-0.24	-0.01	0.02
SST (<i>n</i> = 52)						
Intercept	32.29***	6.09	0.19	-3.49***	-1.40	0.40
Linear slope	-0.21	-0.01	0.06	3.32***	0.31	0.09
Quad. Slope	0.98	0.01	0.01	-2.76**	-0.03	0.01
Recovery (<i>n</i> = 51)						
Intercept	38.34***	6.72	0.18	-3.08**	-1.14	0.37
Linear slope	0.38	0.01	0.03	0.34	0.02	0.05
HR						
Baseline (<i>n</i> = 52)						
Intercept	37.83***	70.69	1.87	3.58***	12.71	3.56
Linear Slope	-1.66	-0.15	0.09	1.69	0.20	0.12
SST (<i>n</i> = 52)						
Intercept	44.37***	79.73	1.80	2.63**	9.44	3.59
Linear slope	3.81***	2.45	0.64	-1.62	-1.27	0.79
Quad. Slope	-3.93***	-0.32	0.08	1.41	0.14	0.10
Recovery (<i>n</i> = 51)						
Intercept	40.24***	73.70	1.83	3.21***	11.65	3.63
Linear slope	-6.18***	-1.31	0.21	-0.10	-0.03	0.29
MAP (<i>n</i> = 54)						
Baseline						
Intercept	82.25***	88.21	1.07	1.29	2.10	1.63
Linear Slope	-3.49***	-0.47	0.14	-0.21	-0.04	0.17
SST						
Intercept	72.29***	91.89	1.27	0.69	1.35	1.96
Linear slope	7.65***	3.99	0.52	-3.08**	-2.56	0.83
Quad. Slope	-5.89***	-0.41	0.07	2.47*	0.24	0.10
Recovery						
Intercept	76.84***	91.66	1.19	0.59	0.96	1.63

Outcome	Control Z	Control <i>b</i>	Control <i>SE</i>	Bipolar Z	Bipolar <i>b</i>	Bipolar <i>SE</i>
HF-HRV						
Linear slope	-3.57***	-0.64	0.18	-0.70	-0.17	0.25
Cortisol (<i>n</i> = 55)						
Intercept	12.25***	10.47	0.86	-2.86**	-3.05	1.07
Linear slope	1.43	1.10	0.77	-2.60**	-2.19	0.84
Quad. Slope	-1.87	-0.36	0.20	2.67**	0.56	0.21

Note. Intercepts represent starting values, and linear and quadratic slopes represent change in values over time. Z-scores and beta-weights listed for controls indicate difference from zero in the control group; those listed for the bipolar group indicate differences in the bipolar group relative to the control group. One participant did not have HF-HRV or HR data during recovery and was therefore omitted from these analyses.

p .001

**
p .01

*
p .05.

Table 3

Z-scores for associations between medication load at initial assessment and physiological responses during social stress in adolescents with bipolar disorder

Outcome	Intercept	Antipsychotics	Mood stabilizers	Stimulants
HF-HRV (<i>n</i> = 24)				
Intercept	14.94 ^{***}	-4.29 ^{***}	-1.82	-2.45*
Linear Slope	-1.19	4.95 ^{***}	1.68	2.59 ^{**}
Quad. Slope	2.21 [*]	-5.52 ^{***}	-1.44	-2.41 [*]
HR (<i>n</i> = 24)				
Intercept	15.35 ^{***}	1.54	-0.26	2.28 [*]
Linear Slope	2.88 ^{**}	-1.34	-0.55	-0.91
Quad. Slope	-3.53 ^{***}	1.56	0.59	0.97
MAP (<i>n</i> = 26)				
Intercept	34.36 ^{***}	1.29	0.79	1.58
Linear Slope	1.10	-1.05	0.80	-0.10
Quad. Slope	-0.83	0.84	-1.31	0.30
Cortisol (<i>n</i> = 27)				
Intercept	6.17 ^{***}	-0.79	0.27	-0.57
Linear Slope	-1.29	0.41	-1.42	1.48
Quad. Slope	0.90	-0.31	1.43	-1.44

Note. Z-scores indicate values when medication load and time equals zero for “Intercept”, change over time during the SST for linear and quadratic slopes, and difference for each unit increase in medication load for “antipsychotics”, “mood stabilizers”, and “stimulants”.

p .001

**
p .01

*
p .05.

Table 4

Associations between depressive symptom severity at initial assessment and physiological response during pre-stress baseline, social stress (SST), and post-stress recovery in adolescents with bipolar disorder.

Outcome	Intercept <i>Z</i>	Intercept <i>b</i>	Intercept <i>SE</i>	MFQ <i>Z</i>	MFQ <i>b</i>	MFQ <i>SE</i>
HF-HRV						
Baseline (<i>n</i> = 23)						
Intercept	13.27***	5.77	0.44	-1.11	-0.02	0.02
Linear Slope	-0.83	-0.02	0.02	1.02	0.00	0.00
SST (<i>n</i> = 23)						
Intercept	9.42***	5.09	0.54	-1.29	-0.02	0.02
Linear Slope	1.87	0.18	0.10	1.95	0.01	0.00
Quad. Slope	-1.11	-0.01	0.01	-1.38	-0.00	0.00
Recovery (<i>n</i> = 22)						
Intercept	14.41***	6.17	0.43	-2.37*	-0.04	0.02
Linear Slope	0.74	0.05	0.06	-0.39	-0.00	0.00
HR						
Baseline (<i>n</i> = 23)						
Intercept	22.84***	81.92	3.59	0.71	0.08	0.11
Linear Slope	0.42	0.05	0.13	-0.24	-0.00	0.00
SST (<i>n</i> = 23)						
Intercept	22.09***	87.20	3.95	0.88	0.10	0.11
Linear Slope	1.66	0.52	0.32	0.37	0.01	0.02
Quad. Slope	-2.10	-0.04	0.02	-0.57	0.00	0.00
Recovery (<i>n</i> = 22)						
Intercept	20.79***	82.30	3.96	1.32	0.18	0.14
Linear Slope	-5.18***	-0.80	0.15	1.64	0.01	0.01
MAP (<i>n</i> = 25)						
Baseline						
Intercept	71.33***	89.43	1.25	0.05	0.00	0.05
Slope	-3.33***	-0.48	0.14	-0.29	-0.00	0.01

Outcome	Intercept Z	Intercept b	Intercept SE	MFQ Z	MFQ b	MFQ SE
SST						
Intercept	49.75***	93.40	1.88	-0.49	-0.03	0.07
Linear Slope	0.52	0.50	0.96	1.32	0.04	0.03
Quad. Slope	-0.54	-0.06	0.11	-1.35	-0.00	0.00
Recovery						
Intercept	71.18***	92.20	1.30	-0.15	-0.01	0.05
Linear Slope	-3.60***	-0.96	0.27	1.04	0.01	0.01
Cortisol (n = 26)						
Intercept	7.64***	6.76	0.89	0.81	0.02	0.02
Linear slope	-1.71	-0.71	0.41	-0.25	-0.00	0.01
Quad. Slope	1.52	0.13	0.09	-0.18	-0.00	0.00

Note. Z-scores and beta-weights indicate values when the MFQ score equals zero for “Intercept”, and difference for each unit increase in MFQ score for “MFQ”. Data for one participant was omitted because she did not complete the MFQ.

*** p .001
 ** p .01
 * p .05.