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Patterns of respiratory sinus arrhythmia and trajectories of anxiety and depressive symptoms in early adolescence

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ABSTRACT

In children and adults, individual differences in patterns of respiratory sinus arrhythmia (RSA; i.e., interactions between resting RSA and RSA reactivity to stress) have emerged as a central predictor of internalizing symptoms. However, it is unclear whether individual differences in patterns of RSA also contribute to internalizing symptoms during the key developmental period of early adolescence, when rates of internalizing symptoms sharply increase. In the present multi-wave longitudinal study, we assessed whether patterns of RSA predicted trajectories of the two most common types of internalizing symptoms among adolescents: anxiety and depression. In the baseline session, we assessed RSA at rest and in response to a psychosocial stressor (Trier Social Stress Test [TSST]) in a sample of 75 early adolescents (M_{age} = 12.85). Youth then completed measures of anxiety and depressive symptoms at baseline and four times over approximately two years. Findings indicate that RSA patterns predicted trajectories of anxiety, but not depression. Specifically, region of significance analyses indicated that individuals with high resting RSA who demonstrated RSA augmentation to the lab stressor evinced decreasing anxiety over the follow-up period. In direct contrast, adolescents with high resting RSA in combination with RSA withdrawal to the stressor exhibited a trajectory of increasing anxiety. Findings provide preliminary evidence for understanding RSA as a developmentally salient risk or protective factor.

Anxiety and depression are the most prevalent mental health conditions worldwide (Friedrich, 2017; Liua et al., 2019) and are associated with increased risk for physical illness and diminished quality of life (Brown et al., 2001; Moussavi et al., 2007; Rapaport et al., 2005). Adolescence is a particularly critical period of vulnerability for internalizing symptoms such as anxiety and depression. The prevalence of symptoms substantially increases during adolescence (Avenevoli et al., 2015; Costello et al., 2003), and an earlier age of symptom onset is associated with increased functional impairment (e.g., social functioning, suicide attempts; Lim et al., 2013; Ramsawh et al., 2011; Zisook et al., 2007) and heightened risk of recurrence (Copeland et al., 2013). However, there remain important differences in the nature of anxiety and depressive symptom trajectories during this developmental period. For instance, anxiety symptom trajectories typically begin in early adolescence and are more likely to decline, in contrast to depressive symptoms, which emerge later and remain stable over time (Cohen et al., 2018; McLaughlin & King, 2015). Given the prevalence and

consequences of anxiety and depressive symptoms, and putative differences in their nature and course, it is critical to understand early markers of risk for each outcome in adolescence.

Aberrant patterns of respiratory sinus arrhythmia (RSA) have emerged as one possible risk factor for symptoms of anxiety and depression. RSA measures fluctuations in heart rate in synchrony with respiration. It is used to index parasympathetic nervous system (PNS) activation and, more specifically, reflects vagal influence on the heart (Thayer & Lane, 2000). This "vagal brake" slows heart rate in the absence of environmental threat (i.e., at rest), suggesting that greater resting RSA corresponds to stronger parasympathetic control over physiological systems at baseline. In the context of threat, however, momentary removal of the vagal brake (i.e., RSA withdrawal) allows for increases in heart rate and mobilization of cognitive and behavioural responses needed to meet environmental demands. Importantly, individual differences in RSA are also thought to be influenced by individual differences in top-down regulation, given putative links between

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top-down neural structures and cardiac activity (Holzman & Bridgett, 2017; Thayer & Lane, 2000). Indeed, consistent with Thayer and Lane's Neurovisceral Integration Model (Thayer & Lane, 2000), inhibitory influence from prefrontal cortical structures modulates parasympathetic influences on the heart. This theoretical account links measures of RSA with self-regulation (i.e., an individual's management of emotions and reactions): whereas resting RSA is correlated with the capacity for self-regulation, RSA reactivity is correlated with self-regulatory responses to an environmental challenge (e.g., a stressor; Beauchaine, 2001; El-Sheikh & Erath, 2011; Rottenberg, 2007). High resting RSA is considered indicative of greater parasympathetic regulatory capacity (Gyurak & Ayduk, 2008; Ode et al., 2010) as it provides a larger range for RSA withdrawal to occur during stress without inducing exceedingly high levels of cardiovascular arousal and before sympathetic activation is needed (Beauchaine, 2001). On the other hand, individuals with lower RSA at rest might experience greater physiological arousal at baseline and, thus, have less capacity for changes in RSA when needed.

Given that psychopathology is strongly linked to aberrant responses to stress, it is unsurprising that individual differences in both resting RSA and RSA reactivity have been associated with internalizing symptoms (Yaroslavsky et al., 2013a). Indeed, several cross-sectional and prospective studies show that lower resting RSA is linked to greater levels of psychopathology in children and adolescents (Forbes et al., 2006; Gentzler et al., 2012; Koenig et al., 2016), and in adults (Yaptangco et al., 2015). Low resting RSA is also associated with greater sensitivity to environments in adults with a history of childhood maltreatment (Skowron et al., 2013), children and adolescents subjected to harsh parenting (Hinnant et al., 2015), and adolescents experiencing low supportive parenting (Mezulis et al., 2015). High resting RSA, on the other hand, has been found to be protective from the development of mental health problems in children following exposure to adverse contexts such as marital conflict (El-Sheikh et al., 2001; Katz & Gottman, 1995) and maternal depression (Blandon et al., 2008). In the context of stress or negative-affect exposure, decreases in RSA (i.e., RSA withdrawal), particularly when moderate (Fortunato et al., 2013; Marcovitch et al., 2010), are cross-sectionally and prospectively associated with adaptive outcomes such as fewer symptoms of psychopathology in children and adolescents (Gentzler et al., 2009; Graziano & Derefinko, 2013; McLaughlin et al., 2014) as well as adults (Panaite et al., 2016; Rottenberg et al., 2003). In contrast, increases in RSA during stress (i.e., RSA augmentation) are cross-sectionally and prospectively associated with maladaptive outcomes, including greater mental health difficulties in children, adolescents (Boyce et al., 2001; Gentzler et al., 2009; McLaughlin et al., 2014), and adults (Beauchaine et al., 2019; Rottenberg et al., 2005). However, other empirical findings are inconsistent. For example, some cross-sectional studies suggest that lower resting RSA, but not RSA reactivity, is associated with greater internalizing symptoms in youth (Dietrich et al., 2007; Zhang et al., 2017); yet, other cross-sectional research in both children and adults has implicated aberrant RSA reactivity, as opposed to resting RSA, in this regard (Bylsma et al., 2014; Fortunato et al., 2013).

Given mixed findings in the RSA literature, it may be important to combine RSA indices when examining associations between RSA and adaptive functioning (Hinnant & El-Sheikh, 2009; Yaroslavsky et al., 2013a). This proposition is supported by empirical and theoretical work. For example, the Neurovisceral Integration Model (Thayer & Lane, 2000; Thayer & Lane, 2009) suggests that the ability to flexibly adapt to one's environment is influenced by biological flexibility, suggesting that the conjunction of resting RSA and RSA reactivity is needed to understand the PNS's contribution to adaptive functioning (Muhtadie et al., 2015). Theoretically, the interaction of resting RSA and RSA reactivity may be particularly adaptive because higher resting RSA provides a greater dynamic space in which greater decreases in RSA (RSA withdrawal) can occur in challenging environments. Empirical studies have also proposed that examining RSA indices independently could obscure important interindividual variability given that individuals with similar

levels of resting RSA may vary in RSA reactivity, or vice versa (Lacey, 1959). As such, the interaction between resting RSA and RSA reactivity may provide a more nuanced account of affective processing than either index alone.

Consistent with this proposition, cross-sectional and prospective studies in both children and adults have found that the combination of high resting RSA and RSA withdrawal predicts adaptive functioning (i. e., less internalizing symptoms), whereas other combinations (e.g., low resting RSA and RSA withdrawal or high resting RSA and RSA augmentation) were associated with maladaptive functioning (i.e., greater internalizing symptoms; Yaroslavsky et al., 2013a, 2013b, 2014). Interestingly, research shows that the combination of resting RSA and RSA reactivity predicts internalizing symptoms beyond the variance explained by either metric on its own (Yaroslavsky et al., 2013a, 2013b, 2014). Thus, examining these indices conjointly may better capture the PNS's role in well-being. Despite the promise of this combined approach, however, there are three main gaps in the empirical literature to date.

First, prospective research on the interaction of resting RSA and RSA reactivity has typically focused on samples of pre-pubertal children ages 6–9 (e.g., El-Sheikh & Arsiwalla, Hinnant, et al., 2011; Hinnant & El-Sheikh, 2009; 2013; Yaroslavsky et al., 2014) or adults (e.g., Yaroslavsky et al., 2013a, 2013b). This focus is surprising given that the onset of internalizing symptoms typically begins in adolescence (Kessler et al., 2007). During adolescence, the onset of internalizing symptoms has been linked to both the greater incidence of external stressors and emergent individual differences in self-regulation. Indeed, the onset of puberty and development of frontal brain regions involved in stress and emotion regulation contribute to maturational changes in stress reactivity (Romeo & McEwen, 2006). Individual differences in these maturational processes may underlie differences in adolescents' ability to effectively mobilize self-regulatory resources in response to normative stressors associated with this developmental period (Lupien et al., 2001). Thus, individual differences in early adolescents' stress reactivity may have implications for the ways in which adolescents cope during this challenging developmental period and, thus, the trajectories of depression and anxiety symptoms that commonly emerge during this time. Moreover, although some work suggests rank-order stability of resting RSA from childhood to adolescence, there is evidence for individual differences in mean levels of RSA reactivity throughout this period (Dollar et al., 2020). As such, associations between patterns of resting RSA and RSA reactivity and the trajectory of psychopathology symptoms may differ according to the age at which they are measured. This possibility underlines the need to understand patterns of RSA associated with trajectories of internalizing symptoms during adolescence.

A second gap in the literature to date is that prior studies have examined either the trajectory of internalizing symptoms more broadly (e.g., combining anxiety and depression) or focused on the trajectory of depressive symptoms exclusively. This approach may explain previously disparate findings for the RSA-symptom association. For example, Yaraslovsky et al. (2014) found that both low resting RSA in combination with greater RSA withdrawal, as well as high resting RSA in combination with RSA augmentation, were most predictive of depression in children. Yet, Hinnant and El-Sheikh (2009) found only low resting RSA in combination with greater RSA withdrawal predicted children's greater internalizing symptoms more broadly. Given that internalizing symptoms typically comprise multiple dimensions, specific patterns of RSA may differentially predict various components of this multi-faceted construct. Although a paucity of research has examined the association of RSA patterns with anxiety symptom trajectories, evidence of different psychophysiological correlates in anxiety versus depression supports the prospect that longitudinal predictors may differ between specific symptom dimensions. Much of this work draws from the tripartite model of anxiety and depression (Clark & Watson, 1991), which posits disparate psychophysiological signatures for each dimension. Psychophysiological hyperarousal is said to be limited to anxiety

(Clark & Watson, 1991), which can manifest as low vagal tone and diminished biological flexibility (Friedman, 2007). Supporting this proposition, Greaves-Lord et al. (2007) found that low resting RSA was concurrently associated with greater anxiety in 10- to 13-year-olds, but not depressive symptoms. In contrast, greater anxiety and depressive symptoms have both been associated with decreased RSA reactivity in this sample (Greaves-Lord et al., 2010). These mixed findings underline the need for additional work to elucidate putative associations between patterns of RSA and trajectories of anxiety versus depressive symptoms.

Finally, although prior work has examined the interaction of resting RSA and RSA reactivity in response to a variety of laboratory tasks such as children's response to a negative mood induction (i.e., a sad film; Yaroslavsky et al., 2014) or a problem-solving challenge (e.g., tracing a star reflected in a mirror; Hinannt & El-Sheikh, 2009), there is currently a limited understanding of the interaction between resting RSA and RSA reactivity in response to social-evaluative stress. Indeed, prior research has examined only resting RSA *or* RSA reactivity in adolescents in response to social-evaluative stress (Aldao et al., 2014; McLaughlin et al., 2014). Given that adolescence is a developmental period characterized by novel social stressors (e.g., forming and navigating new relationships; Benner, 2011; Ganeson & Ehrich, 2009; Isakson & Jarvis, 1999), research is needed to investigate the interaction of RSA during social stress as a potential pathway to trajectories of anxiety and depressive symptoms. In particular, the Trier Social Stress Test for Children (TSST-C; Buske-Kirschbaum et al., 1997) is a well-validated social-evaluative laboratory stressor, which has been shown to have robust and reliable effects on biological markers of stress reactivity (Dickerson & Kemeny, 2004; see Shields & Slavich, 2017). Yet, to our knowledge, no study to date has examined patterns of both resting RSA and RSA reactivity in response to the TSST-C in adolescents, nor associations with both depression and anxiety symptom trajectories across development.

To better understand the key risk and protective factors associated with depressive and anxiety symptoms during a critical period of development, the present study assessed whether interactions between resting RSA and RSA reactivity, in response to a psychosocial stressor, predicted trajectories of anxiety and depressive symptoms across adolescence. We recruited a community sample of early adolescents who were followed for five occasions over approximately two years. Resting RSA and RSA reactivity during the TSST-C were recorded (i.e., at Time 1; baseline), and anxiety and depressive symptoms were self-reported at each time point (Time 1 to Time 5) across adolescence. Moreover, each time point occurred in relation to specific contextual events: prior to the beginning of high school (Time 1), immediately prior to the high school transition (Time 2), the end of students' first semester of high school (Time 3), the onset of the COVID-19 pandemic (Time 4), and approximately 3 months following the onset of the pandemic (Time 5). We anticipated that longitudinal trajectories of anxiety and depressive symptoms would vary according to the interaction between resting RSA and RSA reactivity. Specifically, based on theoretical models and empirical findings (Hinnant & El-Sheikh, 2009; Thayer & Lane, 2000; Thayer & Lane, 2009; Yaroslavsky et al., 2014), we predicted that low resting RSA and greater RSA withdrawal in response to stress, as well as high resting RSA and RSA augmentation in response to stress, would predict increases in depressive symptoms over time. Given the lack of previous research and theoretical models predicting the association between RSA patterns and the trajectory of anxiety symptoms exclusively, we did not make more specific predictions about the nature of this interaction.

1. Method

1.1. Participants

We recruited 11–13-year-old early adolescent youth to participate in the UBC Study of Adolescents prior to beginning high school. We excluded individuals with a history of serious head trauma, medical conditions known to affect the autonomic nervous system (e.g., high blood pressure, hypertension, cardiovascular disease), and/or a diagnosis of a psychiatric condition that was likely to interfere with the completion of the study protocol (e.g., mania, psychosis, substance use disorder). Participants were recruited from the Lower Mainland of British Columbia using recruitment methods designed to facilitate participation from individuals across a diverse range of socioeconomic statuses and racial identities. For instance, we partnered with local school boards and organizations in low- and high-income neighborhoods, and we used online and physical advertisements posted in multiple settings. The final sample included 79 early adolescents between 11.88 and 13.89 years of age. Additional demographic information is presented in Table 1.

1.2. Measures

1.2.1. Symptoms of anxiety

Youth completed the Multidimensional Anxiety Scale for Children (MASC-10; March et al., 1997) to assess symptoms of anxiety. The MASC-10 is a 10-item self-report questionnaire assessing anxiety symptoms in youth between 8 and 19 years of age. It has shown strong psychometric properties in past research (March et al., 1999; Osman et al., 2009), and our reliability estimates for the MASC-10 ranged from $\alpha = .64$ to .81 at each time point. Higher MASC-10 scores indicate greater symptom severity.

1.2.2. Symptoms of depression

Symptoms of depression were assessed using the Centre for Epidemiological Studies Depression Scale for Children (CES-DC; Weissman et al., 1980). The CES-DC is a 20-item self-report measure of depressive symptoms for youth between 6 and 17 years of age. It has shown strong psychometric properties in past research (Doerfler et al., 1988), and our reliability estimates for the CES-DC ranged from $\alpha = .85$ to .93 at each

Table 1
Participant Characteristics.

Age, *M(SD)*	12.85 (0.40)
Sex (% Male)	54
Gender (%)	
Boys	53
Girls	46
Non-Binary	1
Pubertal Stage, *M(SD)*	2.69 (1.07)
Racial Identity (%)	
White	62
Asian	23
Latinx	4
Canadian Indigenous	3
Multicultural	8
Annual Household Income (*n*)	
$20,000-$59,999	4
$60,000-$99,999	11
$100,000-$119,999	9
$120,000-$159,999	17
$160,000 and over	21
Prefer not to answer	17
Primary Caregiver Education (*n*)	
High school diploma	4
College diploma/certificate	10
Bachelor's degree	34
Master's degree	19
Doctorate degree	8
Prefer not to answer	4

time point. Higher CES-DC scores indicate greater symptom severity.[2]

1.2.3. Acute laboratory stressor

To induce a biological stress response, participants completed the Trier Social Stress Test for Children (TSST-C; Buske-Kirschbaum et al., 1997), a standardized psychosocial stressor shown to reliably induce a significant affective and biological (i.e., RSA) stress response in youth (Seddon et al., 2020). The TSST-C protocol followed in the current study was in line with the standardized protocol and with current best-practice guidelines (Buske-Kirschbaum et al., 1997; Linares et al., 2020). Before completing the TSST-C, all participants rested for 15 min while watching a calming nature video (Baseline). Next, participants were given a story prompt and were told that they would finish telling the story out loud in front of a committee of judges (one female and one male). They were told that the committee would monitor their behaviour and rate the quality of their story. Unbeknownst to the participant, this committee was made up of research confederates who were trained to perform this role in a standardized neutral, yet supportive, manner. Further, participants were told that their performance would be video recorded in line with the standard protocol of the TSST-C. Participants were then given 5 min to prepare for the task (Prep). Following this preparation period, participants completed a 10-minute Stressor phase, during which they performed two 5-minute tasks in front of the committee. During the first task, participants were asked to complete the unfinished story that was provided to them during the preparation period. If a participant completed the story in less than 5 min, the confederates asked them to continue. Next, the participant was given instructions to complete an unexpected math task of orally counting backward from 1023 in 13-step sequences. If participants made an error, they were asked to begin again at 1023. Finally, participants rested for 20 min while watching a second calming nature video and then completed a 10-minute debriefing session, thus concluding the Recovery period of the TSST-C.

Affect. To ensure the effectiveness of the psychosocial stressor, self-reported positive and negative affect was assessed using items from the Positive and Negative Affect Scale for Children (PANAS-C; Laurent et al., 1999) at 6 points across the TSST-C: after the baseline period (5 min prior to stressor onset), after the preparation period (immediately prior to stressor onset), immediately following the stressor, and at three points during the recovery period (10–30 min following stressor offset). Consistent with our past work (Jopling et al., 2021), a positive affect composite was calculated by taking the sum of *happy, excited, proud*, and *calm* affect scores, and a negative affect composite was calculated by taking the sum of *stressed, upset, nervous*, and *ashamed* affect scores.

Respiratory Sinus Arrhythmia. To assess RSA, electrocardiograph (ECG) and cardiac impedance were recorded continuously across the TSST-C at a sampling rate of 500 Hz per second, and digitized with a resolution of 24-bits. Data was collected using the MindWare Mobile data acquisition device and Biolab acquisition software (Mindware Technologies Ltd., Westerville, OH). To measure ECG, electrodes were positioned bilaterally to participants' lower rib cage and right collarbone. Cardiac impedance was used to derive respiration (Ernst et al., 1999). Electrodes were positioned on participants' jugular notch (slightly offset from center to prevent an artifact due to speaking) and just below the sternum on the zyphoid process. An additional two electrodes were placed on the spine 1.5 in. above the jugular notch and 1.5 in. below the sternum. The cardiac impedance signal (Z0) is used to validate the RSA data by ensuring that the detected respiration rate falls within the high-frequency band (0.12–0.4 Hz; Berntson et al., 1993).

Several methodologies were used to account for movement during the TSST-C. First, we used service loops when attaching electrodes to participants, which allows the electrode to maintain contact with the skin in the case of movement and minimizes noise in the data. Second,

participants were instructed to minimize movements throughout the experiment and to stand still on an "X" placed on the floor during the TSST-C. Third, a band pass filter (0.25–40 Hz) was applied during the data cleaning phase to reject baseline wander and muscle activity. Fourth, when cleaning the data, we incorporated information from confederates, experimenters, and video analysis to exclude any portions of the data that could have been affected by movement artifacts.

Data were analyzed using MindWare's BioLab analysis software in 60-second increments. The IBI time series was derived by interpolation (Bernston et al., 1995), and a Fast Fourier Transform was used to derive spectral distribution. R-wave markers in the ECG signal were evaluated for artifacts using the MAD/MED artifact detection algorithm implemented in MindWare software and through visual inspection. Identified artifacts were then manually corrected. Following artifact correction, minute-by-minute estimates of RSA were determined. For each minute, we examined the respiration rate to ensure that it was within the high-frequency band (0.12–0.4 Hz). Data cleaning procedures revealed five one-minute segments belonging to five different participants that had respiration rates outside of the acceptable band, and were therefore not usable. All other data were in the acceptable range.

Resting RSA was calculated by taking the average of the last 5 min of the baseline period. RSA reactivity was calculated by computing a standardized residual change score. Compared to simple difference scores, standardized residual change scores reduce additive unreliability and are frequently used in current physiological research (Burt & Obradović, 2013; Stange et al., 2020). To calculate the standardized residual change score in the present study, average RSA values across the 10-minute stressor phase of the TSST-C (including both the speech and math task) were regressed on resting RSA, and the standardized residual was saved for future analyses; lower scores equal greater withdrawal.

1.2.4. Covariates°

To assess variables known to affect responses of the PNS and internalizing symptoms, participants completed a brief demographics questionnaire assessing age, sex assigned at birth, and gender identity. Youth also completed the Tanner Staging Questionnaire (Marshall & Tanner, 1968) to assess pubertal stage. In line with previous work, Tanner scores for each participant were averaged to compute an index of average pubertal development (Dorn et al., 2006). In addition, youth's primary caregiver completed a brief demographics questionnaire assessing youth's racial identity, medication use, and household income.

1.3. Procedure

The present study utilized a longitudinal, multi-session design to assess RSA and trajectories of symptoms of anxiety and depression across the transition to high school. At baseline (Time 1), which took place during their last year of elementary school, participants and their primary caregiver came to the laboratory. Youth completed the TSST-C and assessments of pubertal stage, symptoms of anxiety and depression, and a brief demographic questionnaire. Youth's primary caregiver simultaneously completed a brief demographic questionnaire. Subsequently, youth reported on symptoms of anxiety and depression the month prior to starting high school (Time 2), in December of their first year of high school (Time 3), in June of their first year (Time 4), and at a final follow-up in May-June 2021 (Time 5), which was up to 24 months after participants' baseline assessment. Data collection took place before and during the COVID-19 pandemic. Time between the youth's initial laboratory session and data collection points was an average of 4 months (124 days; *SD* = 89; Time 2), 8 months (232 days; *SD* = 90; Time 3), 13 months (405 days; *SD* = 89; Time 4), and 24 months (718 days; *SD* = 136; Time 5). Youth completed an average of 4 out of 6 time points (*total observations* = 292). All data were assumed to be missing at random (MAR) as missingness was not consistently correlated with scores on the MASC or CES-DC across all time points, *ps* ≥ .106. Missingness was also

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[2] One participant did not provide CES-DC data and, thus, was not included in analyses predicting trajectories of depression.

not associated with racial identity ($p = .079$), sex ($p = .386$), or medication use ($p = .149$).

1.4. Planned analyses

1.4.1. Manipulation check

To ensure the TSST-C induced the expected affective and biological stress response, three repeated measures analysis of variances (ANOVAs) were conducted. First, one-way repeated-measures multivariate ANOVAs were conducted to examine differences in positive and negative affect at baseline (Affect #1) and during the stressor (Affect #2). Second, a one-way repeated-measures ANOVA was conducted to examine differences in RSA during the baseline and stressor periods.

1.4.2. Main analyses

The present study involves nested levels of analysis, with time nested within participants. Thus, a hierarchical linear modeling (HLM) approach was used to examine associations between RSA and trajectories of symptoms of anxiety and depression. Coefficients, variance components, and robust standard errors were based on a sample size of 79 at Level 2, which exceeds best-practice recommendations of sample sizes for the calculation of unbiased estimates in HLM (Maas & Hox, 2005). Linear and quadratic models were evaluated for symptoms of both anxiety and depression, and we selected the models that best fit the data based on Akaike's Information Criteria (AIC) values, deviance statistics, and visual inspection of the symptom trajectories. Specifically, two independent models examined the association of symptoms of anxiety (Model 1) and depression (Model 2) at Level 1, with respiratory sinus arrhythmia variables (i.e., resting RSA, RSA reactivity, and their interaction) at Level 2. Prior to including RSA variables at Level 2, we tested a series of covariates known to influence resting levels of RSA (i.e., age, sex, and medication use) and those known to influence internalizing symptoms (e.g., age, gender, and pubertal stage; Costello et al., 2003; Jiang et al., 2021; Reardon et al., 2009; Twenge & Nolen-Hoeksema, 2002) and retained significant covariates in the final model. Main effects were examined before adding the interaction term. Significant interactions were followed up with region of significance (RoS) and simple slope analyses (Preacher et al., 2006). Following recommendations put forth by Raudenbush and Bryk (2002), robust standard errors were used for all analyses to reduce bias.

2. Results

2.1. Manipulation check and preliminary analyses

The acute laboratory stressor successfully induced the expected significant increase in negative affect and decrease in positive affect from the baseline to stressor period, $Fs \geq 68.35$, $ps \leq .001$, partial $\eta^2 s \geq .480$ (see Fig. S1 in the online supplement). Similarly, there was a significant decrease in RSA from the baseline to stressor period, $F(1, 78) = 49.79$, $p \leq .001$, partial $\eta^2 = .390$ (see Table S1 in the online supplement). Thus, the TSST-C induced the expected affective and biological stress response. Correlations between study variables are presented in Table S2 in the online supplement.

2.2. Main analyses

2.2.1. Symptoms of anxiety

In line with previous work (LeMoult et al., 2015), we first examined mean values and variability in symptom levels over time (see Table S3 and Figure S2 in the online supplement). Given that there was high variability in change in anxiety symptoms over time (average mean difference =.33, average $SD = 4.52$), we examined both linear and quadratic trajectories of anxiety symptoms. The quadradic model (AIC = 1654.17) did not significantly improve model fit beyond the linear model (AIC = 1653.11), $\chi^2(3) = 5.94$, $p = .113$, and visual inspection of

anxiety symptoms over time revealed a linear pattern.

Prior to including RSA variables at Level 2, the aforementioned variables were

tested as potential covariates; none were associated with resting RSA, $ps \geq .289$, or with symptoms of anxiety at baseline or with the linear slope of symptoms, $ps \geq .179$. Therefore, only resting RSA, RSA reactivity, and their interaction were included at Level 2. Results indicated that resting RSA was not significantly associated with anxiety at baseline, $B = -0.20$, $t(76) = -0.44$, $p = .662$, or over time, $B = -0.08$, $t(76) = -0.61$, $p = .544$. Similarly, RSA reactivity was not significantly associated with anxiety at baseline, $B = -0.13$, $t(76) = -0.25$, $p = .801$, or over time, $B = -0.24$, $t(76) = -1.48$, $p = .142$. There was, however, a significant interaction between resting RSA and RSA reactivity in predicting the trajectory of anxiety symptoms, $B = -0.39$, $t(75) = -2.61$, $p = .011$.[3]

Region of significance analyses were used to examine the interaction between resting RSA and RSA reactivity. Analyses indicated that high resting RSA and greater RSA withdrawal (i.e., RSA withdrawal at or below a standardized residual score of -0.75) was associated with symptoms of anxiety increasing over time. In contrast, high resting RSA and *less* RSA withdrawal (i.e., RSA augmentation greater than or equal to a standardized residual change score of 1.03) was associated with symptoms of anxiety decreasing over time. Finally, among youth with low resting RSA, neither RSA withdrawal nor RSA augmentation was significantly associated with trajectories of anxiety symptoms, $p \geq .330$. To visualize these findings simple slopes are presented in Fig. 1, estimating anxiety scores $+/-$ 1 SD from the mean of resting RSA and RSA reactivity.

2.2.2. Symptoms of depression

We first examined mean values and variability in symptom levels over time (LeMoult et al., 2015; see Table S3 and Figure S2 in the online supplement). Given that there was high variability in change in symptoms of depression over time (average mean difference = 3.75, average $SD = 9.66$), we examined both linear and quadratic trajectories of depressive symptoms. The quadradic model (AIC = 2021.07) did not significantly improve model fit beyond the linear model (AIC = 2021.37), $\chi^2(3) = 0.63$, $p = .097$, and visual inspection of depressive symptoms over time revealed a linear pattern.

Before including RSA variables at Level 2, a series of variables were tested as possible covariates. None of the relevant potential covariates were associated with resting RSA, $ps \geq .289$, or with symptoms of depression at baseline or with the linear slope of symptoms, $ps \geq .065$. Thus, only resting RSA, RSA reactivity, and their interaction were included at Level 2. Findings indicated that resting RSA, RSA reactivity, and their interaction were not significantly associated with symptoms of

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[3] We also considered the impact of respiration on our findings by developing RSA indices controlling for within-subject differences in respiration (i.e., resting RSA controlling for resting respiration, RSA reactivity controlling for respiration reactivity, and the interaction of these two new variables that control for respiration). When analyses predicting symptoms of anxiety were repeated using these indices, the pattern of findings did not change and the interaction between resting RSA and RSA reactivity remained significant, $B = -0.38$, $t(73) = -2.59$, $p = .012$. When RSA was replaced with heart rate in the model predicting symptoms of anxiety, the main effect of resting heart rate, the main effect of heart rate reactivity, and their interaction were not significantly associated with symptoms of anxiety either at baseline or over time, $Bs \leq |0.22|$, $ts \leq |1.22|$, $ps \geq .226$.

Simple Slopes of Anxiety at Different Levels of Resting RSA and RSA Reactivity.
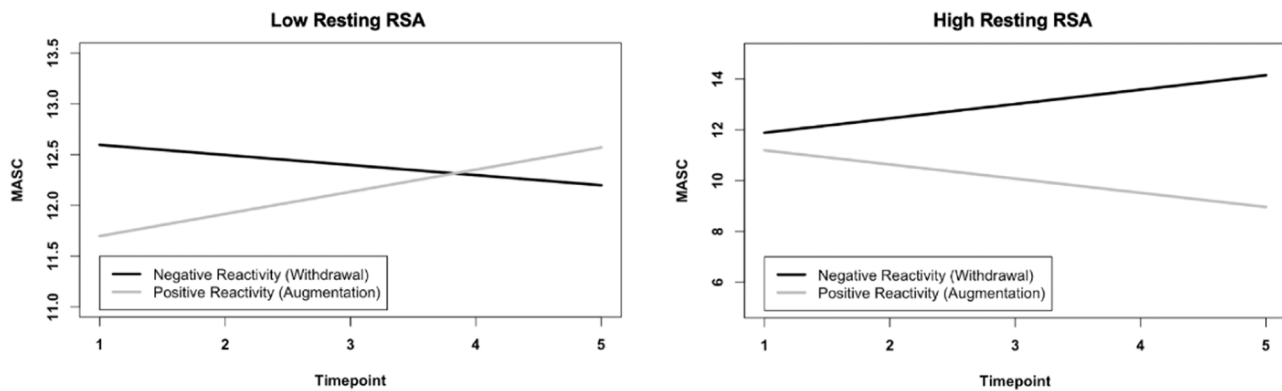
Note. MASC = Multidimensional Anxiety Scale for Children.

Fig. 1. Simple Slopes of Anxiety at Different Levels of Resting RSA and RSA Reactivity. Note MASC=Multidimensional Anxiety Scale for Children.

depression at baseline or over time, $Bs \leq |2.17|$, $ts \leq |1.93|$, $ps \geq .057$.[4]

3. Discussion

The current study was the first to examine the prospective association of patterns of adolescents' resting RSA and RSA reactivity to a stressor with changes in anxiety and depression symptoms over time. Consistent with hypotheses, trajectories of anxiety over a two-year follow-up varied based on the interaction of resting RSA and RSA reactivity. Whereas reactivity did not prospectively predict changes in anxiety among adolescents with *low* resting RSA, reactivity was significantly associated with anxiety among those with *high* resting RSA. Specifically, region of significance analyses indicated that individuals with high resting RSA who demonstrated RSA augmentation to the lab stressor greater than or equal to a standardized residual score of 1.03 evinced decreasing anxiety over follow-up. In direct contrast, adolescents with high resting RSA in combination with RSA withdrawal to the stressor at or below a standardized residual score of − 0.75 exhibited a trajectory of increasing anxiety. RSA did not predict changes in depression over time.

The current results add to a growing body of research demonstrating that parasympathetic regulatory ability as indexed by RSA represents a key mechanism underlying changes in psychopathology. Importantly, and consistent with recent work (Hinnant & El-Sheikh, 2009; Yaroslavsky et al., 2013a, 2013b, 2014), evidence suggests that it is not sufficient to examine a single index of RSA in isolation. Rather, the confluence of resting RSA and RSA reactivity is central for determining trajectories of symptom outcomes. In the current study, reactivity was only a predictor of anxiety among those with *high* resting RSA. Importantly, high resting RSA is considered indicative of greater parasympathetic regulatory capacity (Gyurak & Ayduk, 2008; Ode et al., 2010) because it confers a larger dynamic space for RSA reactivity to occur in response to a stressor. Because RSA reactivity scores can be susceptible to floor and ceiling effects (Hinnant et al., 2015; Rottenberg et al., 2005), RSA reactivity to stress exposure may be impactful for predicting anxiety only among individuals with this enhanced dynamic regulatory range, so long as resting RSA levels are not high enough to

create a ceiling effect in which RSA augmentation cannot occur.

The specific direction of findings for RSA reactivity was unexpected. Past research has documented that low resting RSA in combination with greater RSA withdrawal in response to stress, and high resting RSA in combination with RSA augmentation, predicts greater depression or internalizing symptoms, whereas high resting RSA in combination with RSA withdrawal predicts reduced depression (Yaroslavsky et al., 2013a, 2013b, 2014; Hinnant & El-Sheikh, 2009). However, in the current study, high resting RSA in combination with RSA augmentation predicted decreasing anxiety over follow-up. Conversely, high resting RSA in combination with greater RSA withdrawal prospectively predicted increases in anxiety. Interestingly, however, patterns of RSA were not associated with trajectories of depression in the present study, suggesting specificity in our results. Importantly, past studies (Hinnant & El-Sheikh, 2009; Yaroslavsky et al., 2013a, 2013b, 2014) differ from the current work in that they examined patterns of resting RSA and RSA reactivity as a predictor of depression or of internalizing symptoms more broadly. While frequently co-occurring with depression, anxiety is phenomenologically distinct and has unique physiological correlates (e. g., heart rate variability, RSA; Greaves-Lord et al., 2007, 2008). Thus, we were able to investigate associations of patterns of RSA with anxiety that are unique from those previously documented for depression and the overarching construct of internalizing symptoms. In doing so, the current study begins to address critical gaps in the literature and extends our understanding of the RSA-psychopathology link.

Importantly, the current study also differs from prior work in terms of sample age. Whereas Yaroslavsky et al., (2013a, 2013b, 2014) examined patterns of RSA as a predictor of depression in adults and children, Hinnant and El-Sheikh (2009) examined RSA as a predictor of internalizing in children. However, early adolescence is a period of development during which anxiety may be more salient than depression. For example, anxiety symptoms and disorders tend to emerge at a younger age compared to depression, becoming more common during pre- and early adolescence and demonstrating homotypic continuity across these developmental periods (Beesdo et al., 2009; Cohen et al., 2018). Depression, on the other hand, tends to emerge in adolescence to early adulthood (Kessler & Wang, 2008) and shows trajectories of not only homotypic continuity, but also heterotypic continuity, in which adolescent depression emerges following earlier anxiety (Cohen et al., 2018). Together, these differences in symptom trajectories and prevalence during early adolescence underscore the salience of anxiety during this period and may partly explain our significant findings for anxiety but not depression. Importantly, RSA reactivity also shows normative changes across development – it increases in early childhood before stabilizing in adolescence, and subsequently declines across the

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[4] When respiration was included in the model predicting symptoms of depression, the pattern of findings did not change and all main and interaction effects remained not significant, $Bs \leq |2.28|$, $ts \leq |1.93|$, $ps \geq .057$. When RSA was replaced with heart rate in the model predicting symptoms of depression, the main effect of resting heart rate, the main effect of heart rate reactivity, and their interaction were not significantly associated with symptoms of depression either at baseline or over time, $Bs \leq |0.70|$, $ts \leq |1.66|$, $ps \geq .101$.

adolescent to adulthood transition (Hinnant et al., 2011; Hollenstein et al., 2012). Moreover, during adolescence, RSA may be influenced by a number of maturational factors that are in flux across this developmental stage, including pubertal and biological changes and increases in stress exposure and reactivity (Hamilton & Alloy, 2016). Thus, the present findings for patterns of resting RSA and RSA reactivity and their prospective associations with anxiety, but not depression, may be specific to this critical period of development.

Another factor that may explain differences between our findings and past research examining patterns of resting RSA and RSA reactivity is the type of laboratory stressor used. Whereas the current study used a social-evaluative stressor, Yaroslavsky et al., (2013a, 2013b, 2014) employed a sad mood induction whereby participants watched a sad film clip, and Hinnant and El-Sheikh (2009) used a passive social stressor in which participants listened to an audio recording of adults arguing, as well as a cognitive stressor in which participants completed a star-tracing task while looking through a mirror. Each of these stressors varies along several dimensions, including how passive versus active they are, whether they involve a social component, whether they involve performance or evaluation, and whether they are intended to evoke specific emotions (e.g., sadness) versus general stress. Earlier work has documented that physiological responses vary based on some of these dimensions (Dickerson & Kemeny, 2004). For example, past research suggests that associations of RSA reactivity with clinical symptoms are specific to the emotion elicited by the lab stressor. In particular, exaggerated RSA withdrawal to both fearful and sad, but not happy or angry, emotion inductions was associated with greater internalizing, but not externalizing, symptom severity (Fortunato et al., 2013). Although Fortunato et al. (2013) did not disentangle anxiety from depressive symptoms, their findings highlight that the affective valence of a task used to assess RSA may be uniquely associated with particular symptom clusters. Given that the TSST-C is designed to elicit fear rather than sadness (National Institute of Mental Health, 2023), an emotion more strongly tied to anxiety, this may explain in part why RSA responses were only relevant for predicting anxiety in the current study. Thus, stressor type may represent a key moderator of the association between RSA and psychopathology. Future research investigating associations of patterns of resting RSA and RSA reactivity to various types of stressors within the same sample will be imperative to understanding the link between physiological regulatory responses and symptoms of psychopathology. Similarly, research examining RSA reactivity to daily, naturalistic stressors that occur outside of the laboratory will be valuable for enhancing generalizability across the full range of stressors individuals experience in their day-to-day lives.

Characteristics of the TSST-C may also explain the unexpected finding that, in the context of high resting RSA, greater RSA augmentation – indicative of increases in parasympathetic activity – predicts a trajectory of reductions in anxiety. First, it is important to note that the TSST-C requires participants to speak as they deliver their speech and perform the mental arithmetic task, and prior work has found that speech is associated with a higher RSA amplitude (Reilly & Moore, 2003). Thus, our finding for RSA augmentation may represent an artifact of physical task demands, though this appears unlikely given that we (a) placed electrodes slightly off-center of participants' jugular notch to prevent artifacts due to speaking, (b) accounted for respiration rate, including while speaking, by using the cardiac impedance signal to confirm HRV was in the high-frequency range, and (c) minimized the influence of physical movement in our approach to both the collection and analysis of RSA data. Second, the TSST-C is an active social stressor, and researchers have suggested that the PNS is central to the social engagement system. Specifically, in the context of social situations, RSA augmentation is linked with social support receipt and facilitates prosocial engagement with social partners (Butler et al., 2014; Hastings & Kahle, 2019; Zhang et al., 2004), which could have facilitated the observed trajectory of reduction in anxiety. Third, it is possible that some adolescents may interpret the TSST-C as a challenge rather than as

a threat. Indeed, past research using the TSST-C has found variability in children's appraisals of the task (Erni et al., 2012), and challenge and threat appraisals have been associated with PNS activity (Tomaka et al., 1997). Furthermore, greater emotion regulation strategy use during stress, including strategies that have a direct effect on appraisals (i.e., reappraisal), has been associated with greater RSA augmentation (Davis et al., 2016; Musser et al., 2013; Perry et al., 2012). Considering that the current study did not assess participants' appraisals of the stressor, future research should examine whether challenge appraisals of the TSST-C drive an increase in RSA among some individuals, as well as whether this increase is associated with decreasing levels of anxiety over time. Finally, given that anxiety is characterized by physiological hyperarousal (Clark & Watson, 1991), it is plausible that a tendency to respond to stress with increased parasympathetic activity (i.e., RSA augmentation) may be associated with reductions in anxiety symptoms.

The current findings should be interpreted in the context of this study's limitations. The present study recruited a community sample of adolescents. Although we were able to examine depression and anxiety symptoms along a continuum, consistent with taxometric evidence that these variables represent dimensional constructs (Hankin et al., 2005; Haslam et al., 2012), future research will need to replicate the current findings in a clinical sample. It is also important to note that some follow-ups occurred during the COVID-19 pandemic, and it is unclear to what extent this major global event and associated disruptions to youth's lives may have impacted trajectories of anxiety and depression. Additionally, although we collected information on a number of important covariates associated with RSA (e.g., age, sex, medication use), we did not assess physical fitness or participants' body mass index (BMI). Another important consideration is that, although RSA is frequently considered to be an indicator of self-regulation to stress, the link between RSA and psychological self-regulatory processes, such as emotion regulation, is correlational in nature. It is therefore important not to interpret the current findings for RSA as evidence for the role of psychological self-regulation to stress in predicting anxiety or depression. It is also important to note that RSA values reflect relative changes in vagal motor neurons' responsiveness across a respiration cycle (rather than a complete absence of vagal inhibition during expiration or a complete vagal inhibition during inspiration). As a result, modulation of central vagal activity alters only a small fraction of total influence of the vagus nerve on the sinoatrial node (Eckberg, 2003). Finally, given the novelty of the current findings, and considering that interactions of resting RSA and RSA reactivity have not previously been examined among adolescents or in predicting anxiety, the present findings will need to be replicated in larger, more generalizable samples.

Despite these limitations, the findings reported here represent an important first step in understanding the association of RSA with trajectories of anxiety and depression over time in youth. The present study is the first to suggest that, among early adolescents, and in combination with high resting RSA, RSA reactivity represents both a risk and a protective factor for predicting trajectories of anxiety during a key developmental period. In contrast, patterns of RSA did not predict changes in depression over follow-up. Results highlight the importance of examining resting RSA and RSA reactivity in tandem. Furthermore, given that early adolescence is a critical period of neuronal maturation and plasticity, as well as a time during which anxiety tends to emerge (Beesdo et al., 2009; Kessler & Wang, 2008), it is also an ideal period for prevention and early intervention. If replicated, the current findings suggest that interventions targeting physiological responses to stress may have implications for youth's long-term trajectories of anxiety. Together, results inform our understanding of the unique patterns of physiological regulatory abilities that prospectively predict anxiety and depression in early adolescence.

Declaration of Competing Interest

We do not have any interests that might be interpreted as influencing

the research.

Data Availability

Data will be made available on request.

Acknowledgements

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopsycho.2023.108723.

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