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Examining the Interaction between Stress Exposure and Stress Reactivity as Predictors of Reward Sensitivity and Anhedonia Symptoms

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Abstract

There is a well-documented relationship between stress and depression, although only recently has the field begun to articulate clear models regarding how stress exerts this effect. One prominent model highlights the disruptive impact of stress on reward processing, which relates to anhedonia – a cardinal symptom of depression. Vulnerability-stress models also play an important role in depression research and hold that individual differences in responses to stress may exacerbate the relationship between stress and depression. Pre-ejection period (PEP) reactivity to reward has been posited as an index of reward sensitivity and approach motivation and has been increasingly linked to depression. However, little research has examined the pathways to disrupted PEP responding. The current study examined PEP reactivity to reward as a mediator between stress and self-reported anhedonia symptoms. In addition, I examined whether individual differences in respiratory sinus arrhythmia reactivity to stress affected the impact of stress on PEP reactivity to reward. Participants were 72 youth, ages 11-15 years (M = 13.28, SD = 0.80). Adolescents completed two visits approximately 6 months apart. During the first visit, youth completed a stressor task while RSA reactivity was recorded. At the follow up visit, youth reported on their stress exposure and depressive symptoms, and they completed a reward activity during which PEP reactivity was assessed. The results of the simple mediation examining the effects of stress on PEP reactivity and anhedonia was not significant (Index of mediation = 0.05; CI [-0.20, 0.15]). There was support for the moderated mediation which examined the interaction between stress reactivity and

stress exposure predicting differential effects on PEP reactivity to reward (Index of moderated mediation = -0.11, CI [-0.27, -0.01]). Specifically, stress exposure had a stronger effect on PEP reactivity for youth displaying increased RSA withdrawal to stress while youth with lower levels of RSA responding exhibited no effect of stress on PEP reactivity (b = -2.17; p = .05). In turn, those with smaller PEP changes to reward reported greater anhedonia symptoms (b = .05; p = .04). Although the findings of the study should be considered tentative, the pattern of results appears consistent with theoretical expectations and offer important implications for future research examining PEP and reward sensitivity.

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CHAPTER I

Introduction

Purpose

Anhedonia is a cardinal symptom of depression and refers to a decrease in interest or pleasure in response to previously rewarding stimuli (American Psychiatric Association, 2013). In addition, anhedonia is marked by impaired motivation, reinforcement learning, and reward-based decision-making (Pizzagalli, 2014; Treadway & Zald, 2011). Stress has a well-established association with the onset and duration of anhedonia (Hammen, 2005). However, the potential physiological mechanisms through which this relationship occurs are less understood. One potential pathway may be through the impact of stress on dopaminergic pathways involved in reward processing; this hypothesis has a strong theoretical basis and empirical support in animal models (see Pizzagalli, 2014). Furthermore, it may be that the impact of stress on dopamine pathways depends on individual differences in how intensely an individual experiences a stressor. As such, a biologically vulnerable individual who responds with a more marked physiological stress response may be at greater risk for anhedonia due to developing stress-induced blunting of the dopamine responses to reward.

An emerging body of research suggests that central dopamine responding to reward may be indexed peripherally by cardiac pre-ejection period (PEP) reactivity to reward paradigms (Zisner & Beauchaine, 2016a). Cardiac pre-ejection period is a measure of the duration of time spanning left-ventricular depolarization to the ejection of blood into the aorta. Changes in PEP are mediated by the sympathetic nervous system (SNS), and SNS responses facilitate both approach and active avoidance behaviors.

Consequently, blunted sympathetic responses to reward conditions, as indexed by less PEP reactivity, are one psychophysiological index of impaired approach motivation. Although several studies have examined the effects of stress on central dopamine functioning in animals, few studies have examined whether this link occurs within humans, and no studies have examined the effects of stress on PEP reactivity to reward. Given the relation between central dopamine and PEP reactivity to reward, it may be that PEP reactivity will be subject to the same negative effects of stress.

Cardiac vagal tone is an index of parasympathetic nervous system (PNS) arousal and has been associated with a wide range of psychopathology (Beauchaine, 2001; Porges, 2007). In theory, individuals exposed to acute stress should display a decrease in parasympathetic regulation, facilitating a global increase in arousal that allows the individual to meet the demands of the environment. However, large decreases in the effects of the PNS may result in physiological hyperarousal (Graziano & Derefinko, 2013). Individuals with such a response may experience a stressor more intensely or be less capable of regulating their response to stress. It may be that individuals displaying this hyperaroused state in response to stress may show greater impacts of this stress on reward processing, thereby increasing the likelihood of experiencing anhedonic symptoms. My dissertation will examine the relationships between stress and anhedonia and the potential mechanistic role of SNS and PNS responses to a laboratory tasks (see figure 1). In the following sections I will review the theoretical foundation for the relationships between these variables.

Depression and Anhedonia

Depressive disorders are the 4th leading cause of disability worldwide (Murray & Lopez, 1996). Although depression in childhood is relatively uncommon, a dramatic increase in depressive disorders occurs during the transition from childhood through adolescence (Avenevoli, Knight, Kessler, & Merikangas, 2008). These early onset depressive disorders are associated with a life-course trajectory characterized by recurrence of depression and greater impairment (Fergusson, Boden, & Horwood, 2007; Fergusson, Horwood, Ridder, & Beautrais, 2005; Johnson, Cohen, & Kasen, 2009), making this a particularly useful period to examine in depression research (Thapar Collishaw, Pine, & Thapar, 2012). Understanding the factors, mechanisms, and pathophysiology leading to the onset of depression is important for developing prevention and treatments for depression (Insel et al., 2010). However, one difficulty in understanding the development of depression is the heterogeneity of the disorder (Fried, Nesse, Guille, & Sen, 2015).

Based on the current diagnostic criteria for depression, there are at least 126 possible combinations of symptoms that could result in a diagnosis. Furthermore, two people diagnosed with depression may share as few as one symptom. Because of this, efforts to find biomarkers or specific mechanisms of action are likely to be less successful when examining depression as a global construct, and this has led researchers to parse out specific symptoms of depression as dependent variables (Hasler, Drevets, Manji, & Charney, 2004; Insel et al., 2010; National Institute of Mental Health, 2003). Anhedonia is one symptom that has been isolated in an attempt to understand depression development in a nuanced manner.

Anhedonia refers emotionally to a decrease in interest or pleasure in response to previously rewarding stimuli (American Psychiatric Association, 2013) and behaviorally is associated with impaired motivation, reinforcement learning, and reward-based decision-making (Pizzagalli, 2014). Anhedonia and its associated motivational deficits refer to a particular endophenotype that may be present with or without the negative valence components of depression (Chen, Eaton, Gallo, Nestadt, 2000). The presence of anhedonia in depression is associated with a particularly unfavorable trajectory marked by elevated risk for future depressive symptoms (Hundt et al., 2007), prolonged time to recovery (McFarland, Shankman, Tenke, Bruder, & Klein, 2006), depression chronicity over 10 years (Moos & Cronkite, 1999), and suicidal ideation and attempts over a 2-year period (Spijker, de Graaf, ten Have, Nolen, & Speckens, 2010). Furthermore, anhedonia is implicated in a broad range of mental health problems including internalizing and externalizing disorders (Bedwell, Gooding, Chan, & Trachnik, 2014; Shankman, Katz, DeLizza, Sarapas, Gorka, & Campbell, 2014). Approximately 76% of depressed adolescents report significant levels of anhedonia (Lewinsohn, Pettit, Joiner, & Seeley, 2003); thus, understanding predictors of anhedonia may significantly aid our understanding of this key symptom in developmental depression research (Forbes & Dahl, 2012).

Stress Predicts Anhedonia

Stress is the most robust predictor of onset and duration of depressive disorders (Hammen, 2005), with greater exposure to stress associated with both greater depressive symptoms as well as clinical diagnoses of depression (Brown & Harris, 1989; Shrout, Link, Dohrenwend, Skodol, Stueve, & Mirotznik, 1989; Rojo-Moreno, Livianos-Aldana,

Cervera-Martínez, Dominguez-Carabantes, & Reig-Cebrian, 2002). Despite this well-established relationship, little is known about the pathophysiological mechanisms behind this association (Hasler, 2010), and even less is understood of the underlying mechanisms linking stress with anhedonia (Thomsen, Whybrow, & Kringelbach, 2015). A recent study found that stress is associated with differential depressive symptom increases, in particular anhedonia increases, with anhedonia/loss of interest exhibiting a disproportionately larger increase than 7 of 8 other depressive symptoms (Fried et al., 2015). This not only further highlights the need for research that is directed at specific symptoms and not diagnostic clusters (Insel et al., 2010), but also raises hypotheses about the unique and specific effect stress may have on the neurological substrates underlying anhedonia specifically. In particular, recently articulated theoretical models linking stress to reward sensitivity responding and anhedonia are finding support in animal research and may provide a framework for explaining the relationship between stress and anhedonia (Pizzagalli, 2014).

Deficits in Reward Sensitivity May be the Mechanism Linking Stress with Anhedonia

Anhedonia reflects disruptions in processing and responding to positive stimuli. There are many ways in which the reward and pleasure deficits observed in anhedonia have been operationalized. An important feature of anhedonia is the loss of motivation to engage in previously rewarding stimuli, and one common way for assessing this deficit is by examining the behavioral and physiological changes elicited by incentives and that are intended to facilitate the activation of the individual to obtain the reward. Some researchers have labeled this *reward sensitivity*. At the same time, the term reward

sensitivity is also used to describe the process of generating reward-based response biases (Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008). Although both are associated with anhedonia, for the purposes of this proposal, I will use the term reward sensitivity to mean the response to rewarding stimuli that results in preparatory physiological changes to obtain (work toward or approach) the incentive. Disruptions in the biological bases involved in reward sensitivity may therefore be a useful predictor of anhedonia.

One key biological basis for reward sensitivity may be the central dopaminergic (DA) pathways that are implicated in reward processing and have become central neurological substrates associated with major depressive disorder (Pizzagalli, 2014). Importantly, central DA transmission is specifically theorized to contribute to both the affective and behavioral aspects of anhedonia (Nestler & Carlezon, 2005). The mesolimbic dopamine pathway is involved in incentive motivation (Berridge, 2007) and behavioral approach (Brenner, Beauchaine, Sylvers, 2005; Gatzke-Kopp et al., 2009), and several neuroimaging and dopamine depletion studies implicate compromised dopamine transmission in the reward insensitivity observed in major depressive disorder (see Pizzagalli, 2014).

One way researchers have assessed central dopamine reactivity to rewards in human participants is by using cardiac pre-ejection period reactivity (PEP; Beauchaine et al., 2007; 2013; Beauchaine & Gatzke-Kopp, 2012; Brenner & Beauchaine, 2011; Brenner et al., 2005). Although basal PEP is subject to influence from multiple autonomic and central nervous system sources, PEP reactivity (i.e., change during a task) is almost exclusively determined by sympathetic (β-adrenergic) influences (Sherwood,

Allen, Obrist, & Langer, 1986) such that increases in sympathetic nervous system arousal correspond to shortening PEP.

The use of PEP reactivity to reward as a proxy for central DA responding follows from extensive theory and research (Zisner & Beauchaine, 2016a). According to Zisner and Beauchaine:

> Approach behaviors, which characterize reward related processes, require energy mobilization, a function subserved by the SNS to meet metabolic demands. Second, changes in cardiac output required for behavioral approach are mediated by SNS-induced increases in the contractile force of the left ventricle (Sherwood et al., 1986). Third, dopamine modulates sympathetic function (Mannelli et al., 1999) and direct infusions of dopamine agonists into midbrain structures produce SNS-mediated increases in cardiac output (van den Buuse, 1998) that are similar to those observed when normal controls participate in reward tasks (see Brenner et al., 2005; Richter & Gendolla, 2009).

Several studies within the externalizing literature provide empirical support implicating PEP reactivity to reward in the etiology and cross-sectional occurrence of psychopathology (Zisner & Beauchaine, 2016a). Given the comorbidity between externalizing disorders and depression (Hink et al., 2013) and neuroimaging studies suggesting similar disturbances in mesolimbic dopamine functioning across these disorders (Forbes, Shaw, & Dahl, 2007; Gatzke-Kopp et al., 2009; Zisner & Beauchaine, 2016a), it stands to reason that similar PEP reactivity to reward may be observed in

depressed individuals reporting anhedonia, a symptom characterized by deficits in reward responding.

Impairments in the integrity of these DA pathways, and by extension, PEP reactivity to reward, may result in anhedonic behaviors, and research into the causes of this disruption suggests stress may play an etiological role (Pizzagalli, 2014). Stress has a complex relationship with dopamine responding, and an extensive review is beyond the scope of this study. Therefore, in the following paragraph I will briefly review evidence for the effects of stress on mesolimbic DA responding.

Because of the difficulty in assessing DA responding and ethical boundaries in human study, research on causal associations between stress and DA responding is primarily restricted to animal research. These studies have utilized both acute and chronic stress paradigms that indicate exposure to greater levels of stress and uncontrollable or inescapable stress is associated with inhibition of, or blunted responding within, mesolimbic dopamine pathways. For example, in a particularly comprehensive study, Bekris and colleagues (2005) examined the impact of chronic mild stress on both preference-based behavior and neurophysiological changes. The results suggest that after several weeks of being exposed to mild stress, rats were less likely to display a preference for a highly palatable sucrose solution, and at the same time displayed lower basal mesolimbic dopamine levels. In addition, another study found that exposure to chronic mild stress resulted in decreased mesolimbic dopamine reactivity to receiving a palatable food (Di Chiara, Loddo, & Tanda, 1999).

Taken together, these studies suggest central dopamine function and anhedonic behavior fluctuate as a function of stress. Thus, the first two hypotheses of this study are

that (1) stress will predict anhedonia and (2) that this effect will be mediated by impaired reward sensitivity, indexed by PEP reactivity to reward.

However, studies have also found that only some rats were susceptible to the effects of stress (Bekris et al., 2005; Rygula, Papciak, & Popik, 2013), suggesting that characteristics of the organism may buffer or exacerbate the effect of stress on dopaminergic systems and anhedonic behavior. Importantly, this line of evidence is wholly consistent with human-based research examining vulnerability-stress models of depression, which posit that preexisting differences in cognitive, physiological, and behavioral reactivity to stress may place certain individuals at greater or lesser risk for depression when confronted with stress (Hyde, Mezulis, & Abramson, 2008). Based on the evidence above, the adverse effects of stress on reward processing and reward sensitivity may be dependent on the characteristics of the stress response of the individual experiencing the stressor. In the following sections I will discuss one such vulnerability that may contribute to the differential impact of stress.

High Physiological Reactivity to Stress May Exacerbate the Effects of Stress on Reward Sensitivity Systems

Vulnerability-stress models are widely adopted frameworks for understanding the etiology of psychopathology (Meehl, 1962; Monroe & Simons, 1991). Vulnerabilities may be present at multiple levels of analysis (i.e. genetic, biological, temperamental, and cognitive) and may have impacts on each other (e.g. high temperamental emotional reactivity may lead to higher cognitive vulnerabilities; Mezulis, Hyde, & Abramson, 2006). In depression, cardiac vagal tone has become an intriguing risk factor and has

garnered increased attention in recent years (Beauchaine, 2015; Beauchaine & Thayer, 2015).

Cardiac Vagal Reactivity to Stress. The autonomic nervous system consists of the sympathetic nervous system and parasympathetic nervous system (PNS) that provide involuntary and primarily reflexive inputs to body organs that facilitate rapid responses to stimuli (Berntson, Quigley, & Lozano, 2007). Polyvagal theory suggests that one function of the PNS is to flexibly promote social interaction and a return to homeostasis when the individual is not experiencing environmental demands (Porges, 2007). During stress, however, there is a withdrawal of PNS-mediated inhibitory influences, enabling the individual to orient rapidly and respond appropriately to the situation. This parasympathetic modulation of arousal (via the nucleus ambiguus) is a sophisticated and more recent evolutionary adaptation that allows mammals to conserve fight-flight resources in favor of affiliative strategies (Porges, 1995).

Parasympathetic nervous system activity is often measured using vagal tone, which refers to the tonic influence of the vagus nerve on the sino-atrial node of the heart (Porges, 1995). The construct of vagal tone can be assessed indirectly using respiratory sinus arrhythmia (RSA), a measure of high frequency variability in heart rate across the breathing cycle (Berntson, Cacioppo, & Grossman, 2007). Under baseline (i.e., resting) conditions, parasympathetic influence should be high and thus higher resting RSA indicates greater physiological flexibility and ability to adapt when faced with environmental stressors (Porges, 1995; 2007). Consistent with this, high resting RSA in youth has been associated with less negative emotionality, more adaptive emotion regulation, social competence, and fewer internalizing and externalizing symptoms (see

Beauchaine, 2001, 2012 for reviews; see also Gentzler, Santucci, Kovacs, & Fox, 2009; Thayer, Friedman, & Borkevec, 1996).

RSA reactivity may index vagal control over the heart that is acutely responsive to fluctuations in environmental demands. When confronted with situations that require the individual to respond, the vagus nerve withdraws its inhibitory effect on cardiac function, facilitating the mobilization of metabolic resources to enact behavioral strategies to respond to the environment. Alternatively, an individual may experience vagal augmentation, consisting of an increase in vagal inhibitory effects. As noted above, there is a normative RSA withdrawal or augmentation in response to stressful situations. However, extreme RSA withdrawal is thought to reflect a sense of hypervigilance or attention to threatening/negative stimuli, and is associated with heightened physical and psychological stress (Graziano & Derefinko, 2013).

RSA Reactivity to Stress and Depression. The relationship between youth RSA reactivity to stress and depression is complex, as most researchers have used broader internalizing scales comprised of anxiety, somatic, and depressive symptoms. Furthermore, the evidence within this internalizing domain is mixed with some researchers finding symptoms to be associated with excessive RSA reactivity and others finding a relationship with RSA augmentation (see Graziano & Derefinko, 2013). It is worth noting that these studies have investigated cross-sectional and longitudinal main effects, and it may be that stress reactivity as an individual difference variable may moderate the effects of stress exposure on health. That is, an individual with an extreme physiological stress response who is exposed to low levels of stressful events may not show the same level of negative outcomes as a similar person in a high stress

environment.

Another limitation may be the broad associations between one index of stress reactivity and the broad measures of internalizing symptoms. As reviewed in the previous sections, heterogeneity in mental health disorders may mask important nuances in the relationships between predictors and outcomes. Internalizing symptom scales incorporate several domains of functioning and it is not likely that all symptoms within the mulitfactorial umbrella share a precise, common biological background (Fried, Tuerlinckx, & Borsboom, 2014; Insel, et al., 2010). Moreover, these associations do not inform researchers of the potential mechanism or pathways to the disorder. Examining specific symptoms of depression, such as anhedonia, may help to clarify some of these mixed findings and additionally shed light on the mechanisms in which stress may lead to these symptoms.

The Current Study

The heterogeneity of depression has made examinations of its etiology a difficult research endeavor. Anhedonia is a hallmark symptom of depression and has increasingly become a focus of depression research. Extant research demonstrates clear associations between stress and anhedonia, between central nervous system mediated reward sensitivity and anhedonia, and the deleterious impacts of stress on these reward sensitivity substrates. Thus, I hypothesize that stress will predict decreased reward sensitivity (indexed by PEP reactivity to reward) which will in turn predict greater anhedonia. Further, vulnerability-stress models suggest that individual differences in stress reactivity may amplify the effects of stress on downstream outcomes such as reward sensitivity. Consequently, I also hypothesize that the positive effect of stress on

reward sensitivity will be moderated by stress reactivity (indexed by RSA reactivity to stress; see Figure 1) such that greater RSA reactivity scores will result in larger effects of stress on reward sensitivity.

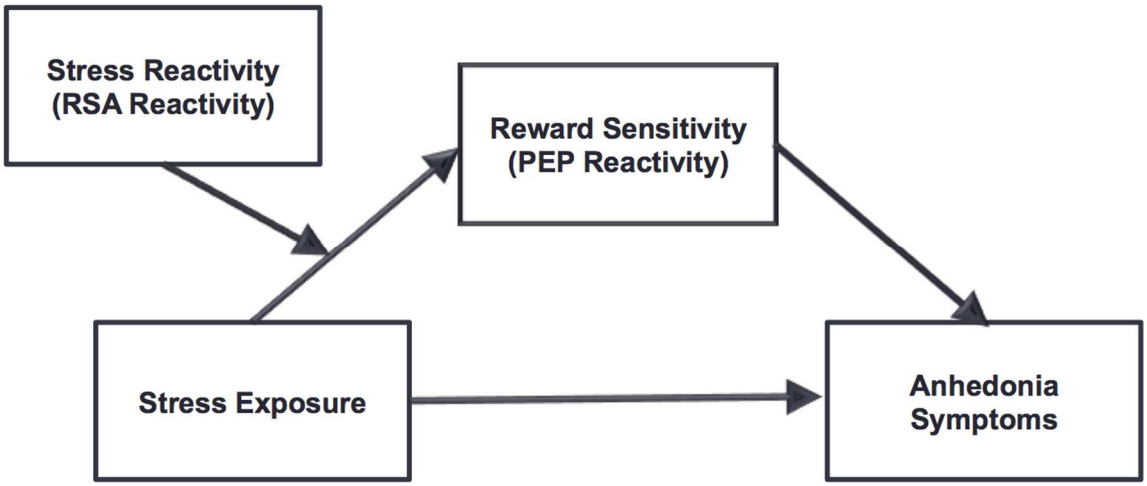

Figure 1. Conceptual moderated mediation model.

CHAPTER II

Method

Sample and Participant Selection

Participants. Participants were 141 (53% female) youth ages 11-15 years (M = 13.28, SD = 0.80) enrolled in public schools in the Pacific Northwest. Approximately 79% were Caucasian; 8% were Asian-American; 1% were African-American; 12% identified as biracial or other. Youth were invited to participate in the school-based screening if they were (1) 10 to 14 years old; (2) in 5th to 8th grades; and (3) if they and one parent were sufficiently fluent in English to complete study questionnaires. Parents provided consent and youth provided assent for screening. Because the purpose of the broader study was to identify prospective pathways to adolescent-onset depression, youth were invited to the laboratory visit only if they reported depressive symptoms below the clinical cutoff (i.e., total score of 13 or lower) on the Children's Depressive Inventory – 2nd Edition (CDI-2; Kovacs, 2010).

A priori statistical power was examined for the mediation model using the guidelines proposed by Fritz and MacKinnon (2007). Using a bias-corrected bootstrapped test of mediation, a sample size of approximately 71 is needed to detect an indirect effect comprised of medium effect sizes on both the alpha and beta path using a power of .80.

Procedure. The Seattle Pacific University institutional review board approved all procedures within this study. Prior to each visit, parent or guardian and youth provided informed consent and assent. Youth were invited to laboratory visit between 4-6 months after screening. At this visit, youth completed self-reported measures on a desktop

computer followed by a stressor task to assess RSA reactivity to stress. First, youth completed a 4-minute baseline period in which they viewed relaxing nature scenes. After this period, they completed a 5-minute anagram stressor task, which consisted of solvable and unsolvable anagrams, designed so that the participant could not get more than 50% correct. Youth were paid $30 and parents were paid $50. In total, 141 youth participated in the laboratory visit. Data from four children were excluded from analyses due to physiological equipment malfunction (*N*=3) and a child declining to participate in the physiological portion (*N*=1).

Approximately six months after the T1 visit, youth were invited to the laboratory visit where they completed self-reported measures and completed the reward task to assess PEP reactivity. Participants first completed a 3-minute vanilla baseline period in which they viewed relaxing nature scenes. Following this, participants were presented with a delayed-matching-to-sample task (Richter & Gendolla, 2009). Participants were instructed that the computer would randomly decide a performance expectation to determine if they would earn an additional $10 gift card following their visit. This reward task and incentive have been shown to reliably produce PEP responses in nondepressed individuals (Richter & Gendolla, 2009). In accordance with research suggesting effort-based tasks be unfixed in difficulty (Wright, Killebrew, & Pimpalapure, 2002), each task was presented until the participant made a response. Participants were cued by the researcher and computer program to try to gain the highest score possible to increase their likelihood of obtaining the card. Regardless of the participant's performance, following the task, the computer informed the participant they had eclipsed the benchmark and would receive the $10 gift card. Youth were paid a total of $20 for

the visit and parents were paid $25.

A total of 141 participants completed the initial laboratory visit. However, the administration of the reward task at the 6-month follow-up was piloted to only a random subsample of the original 141 participants ($N = 95$). Between subjects *t*-tests revealed that the 46 participants that were not administered the reward task did not differ from those who did complete the reward task in terms of demographic, predictor, or outcome variables (all p's > .19). Due to excessive movement artifacts or technical problems (e.g. loosening leads), PEP data were not usable for 19 youth and these participants were not included in the analyses. A final sample that comprised of adolescents with complete physiology data at both T1 and T2 consisted of 72 participants[1].

Measures

Depressive Symptoms. Youth depressive symptoms were assessed with the Children's Depression Inventory – 2nd Edition (CDI-2; Kovacs, 2010). The CDI-2 is a 28-item self-report inventory that inquires about the presence of depressive symptoms within the past two weeks; it is normed for use with youth aged 8 to 17. Each item contains three statements; participants were asked to select the statement that best described them in the previous two weeks. Total scores on the CDI can range from 0 to 54, with higher scores indicating more severe depressive symptoms. The CDI has repeatedly demonstrated excellent internal consistency (alpha reliability ranges from .80 to .87), test–retest reliability, and predictive and construct validity, especially in community samples (Blumberg & Izard, 1986; Kovacs, 1981, 1985). The CDI-2 was administered at screening and youth with scores greater than 14 were not eligible for the follow-up lab visit. Children were re-administered the CDI-2 at the first and second lab

[1] I acknowledge the high percentage of data missing due to technical problems. These problems occurred primarily during the beginning of the data collection and are attributed to the piloting of a new paradigm and data acquisition process. That is, there was not any systematic influence of participant variables on the data collection at the lab visit.

visit. The internal consistency of the CDI-2 at screening was excellent (.88) and at the laboratory visits were adequate (T1 = .79; T2 = .77).

To examine the anhedonia symptom cluster of depression, separate scores were created to reflect anhedonia symptoms and negative emotionality/other depression symptoms. Although the CDI factor structure does not specify a specific anhedonia scale (Kovacs, 2010), previous work indicates specific CDI items may be selected to create an anhedonia and low positive affect symptom scale (Chorpita et al., 1998; Hankin, 2008; Logan et al., 2013; Wetter & Hankin, 2009). In the present study, the six CDI items (numbers 4, 12, 15, 20, 21, & 22; Chorpita et al., 1998) were summed to create an anhedonia scale. The greatest level of endorsement for each of these items was: *I do not want to be with people at all*; *I feel alone all the time*; *I never have fun at school*; *I don't have any friends*; *I have to push myself all the time to do my schoolwork*; *Nothing is fun*. To calculate a score containing the remaining depressive symptoms, the total anhedonia scale was subtracted from the overall CDI score to yield a nonanhedonic depressive symptom score. This symptom cluster consisted of items reflecting negative mood, sleep impairment, and appetite disruptions.

Stress Exposure. Youth exposure to stress was measured at the second visit using the Adolescent Perceived Events Scale (APES; Compas, Davis, Forsythe, & Wagner, 1987). The APES measure is a self-report retrospective checklist that assesses exposure to a broad range of events over the previous 6 months. The version used in this study consisted of 60 items and spanned both major life events such as divorce as well as daily hassles such as getting in arguments or fights with other kids. The APES has been shown to be a valid predictor of internalizing symptoms. Test-retest reliability has been shown

to be adequate (r = .86; Compas et al., 1987).

Pre-ejection Period. Cardiac PEP was derived using electrocardiography and impedance cardiography to determine the time interval between left-ventricular depolarization and the ejection of blood into the aorta. Electrocardiograph data were acquired using a BIOPAC MP150 Data Acquisition Unit and thoracic impedance was acquired using a BIOPAC NICO100C Noninvasive Cardiac Output Module (Goleta, CA) and processed offline using MindWare Technologies IMP 3.0.10 analysis program (Gahanna, OH). Data were visually inspected for incorrect placement of markers by the automated scoring algorithm and corrected as needed by trained research assistants. PEP was ensemble averaged using 30-second epochs. The average PEP value across the three minutes of the vanilla baseline was used to create a single basal PEP score. PEP reactivity to the reward paradigm was determined by first averaging participants PEP across the three minute reward task. Second, change scores were computed by subtracting basal PEP from PEP across reward tasks. Thus, positive change scores reflect a decrease in sympathetic arousal (i.e., lengthening PEP) and negative change values reflect an increase in sympathetic arousal (i.e., shortening PEP).

Respiratory Sinus Arrhythmia (RSA). Youths' cardiac activity was recorded throughout the 4-minute seated resting baseline. All recordings occurred in the same sound-attenuated laboratory suite with standardized temperature and lighting. Participants were asked to refrain from use of caffeine and stimulant medication for 36 hours prior to the laboratory session, and oral confirmation of their adherence to this protocol was obtained from both parent and youth upon arrival. Disposable pre-gelled Ag/AgCl electrodes were placed on the chest and abdomen using a Lead II placement.

Electrocardiograph (ECG) data were acquired continuously using Biopac MP150 Data Acquisition Unit (Goleta, CA) and sampled at 1000 Hz. ECG data were processed offline using MindWare Technologies HRV 3.0.10 analysis program (Gahanna, OH). Data were visually inspected for movement artifacts or incorrect placement of markers by the automated scoring algorithm and corrected as needed by trained research assistants. The resulting inter-beat interval time series was subjected to a fast Fourier transformation by the MindWare software, and power in the respiratory frequency band (.15-.40 Hz) was derived from the spectral density function. RSA values were extracted in 30-second epochs. The average RSA value across the four minutes of vanilla baseline was used to create a single basal RSA score. Range and mean value for baseline RSA were consistent with published literature for community developmental samples (see Table 1; Zisner & Beauchaine, 2016a). RSA reactivity to the laboratory stressor was determined by averaging participants' RSA across the 5 minutes of stressor task. Second, change scores were computed by subtracting basal RSA from RSA across the stressor. Thus, positive change scores reflect vagal augmentation and negative change values reflect vagal withdrawal.

CHAPTER III

Results

Data Preparation Prior to Analysis

Prior to analysis, all data were examined for validity concerns such as patterns of missingness, biological plausibility, and normality. A missing value analysis was performed across the variables for participants who were administered the reward task at T2. Little's chi-square statistic was nonsignificant ($p > .80$), consistent with the assumption that data were missing completely at random. One PEP reactivity outlier was identified. For this participant, the PEP values within both the baseline period and the task period were consistent, and the change score was biologically plausible. Therefore, the outlier change score was winsorized to reduce skew. Analyses of normality indicated several variables were skewed and/or kurtotic (see Table 1). To address the skewness, I elected to use a square root transformation of the depressive symptoms and stress variables.

Table 1
Normality Results for Study Data

	Pre-Cleaning		Post-Cleaning		
Variable	Skew	Kurtosis	Outliers Removed	Skew	Kurtosis
Anhedonia	1.14	0.85	0	0.34	-1.48
NonAnhedonia	1.71	3.02	0	0.31	-0.20
Stress	1.27	2.90	0	0.79	1.09
RSAb	-0.87	2.06	0	--	--
RSAr	-0.46	0.92	0	--	--
PEPb	0.07	-0.72	0	--	--
PEPr	-0.71	0.01	0	--	--

Descriptive Analyses

Means, standard deviations, ranges, and bivariate correlations for study variables are presented in Table 2. Stress was positively correlated with both anhedonia (r = .31) and non-anhedonia (r = .55) depressive symptoms, as well as with baseline PEP (r = .33). Baseline PEP also correlated with anhedonia symptoms (r = .26), while PEP reactivity to reward was marginally associated with anhedonia symptoms (r = .22). Contrary to expectations, sex was not associated with either anhedonia or non-anhedonia depressive symptoms in this sample. Therefore, sex was excluded as a covariate in all analyses. Age was not associated with other variables and likewise was not included in the analyses.

Table 2
Means, Standard Deviations, Ranges, and Correlations

		1	2	3	4	5	6	7	8	9	10	11
1. Sex		-										
2. Age T2		-.01	-									
3. Stress Exposure		.05	.03	-								
4. RSAb		.04	.11	.13	-							
5. RSAt		.08	.02	.04	.82**	-						
6. RSAc		.06	-.14	-.15	-.32**	.27*	-					
7. PEPb		.03	-.06	.33**	-.21	-.26*	.07	-				
8. PEPt		.05	-.06	.31**	-.16	-.23†	-.10	.92**	-			
9. PEPc		.02	-.06	.14	.04	.01	-.05	.17	.54**	-		
10. Anhedonia		-.17	-.17	.31**	-.12	-.03	.16	.26*	.30**	.22†	-	
11. Non Anhedonia		-.09	-.10	.55**	-.10	-.11	-.01	.20	.16	.01	.50**	-
M		-	13.28	23.25	7.09	6.48	-0.60	101.46	100.20	-1.18	0.96	3.32
SD		-	0.80	6.53	1.01	0.99	0.60	6.87	8.38	3.03	1.18	3.60
Range	Min	-	11.87	13.00	3.39	2.81	-2.47	86.50	71.17	-8.67	0.00	0.00
	Max	-	15.07	50.00	9.23	8.50	0.76	115.67	118.67	5.00	5.00	17.00

Note. RSA = Respiratory sinus arrhythmia; PEP = Pre-ejection period; b = baseline average, t = task average, c = change score; Sex coded Female = 0, Males = 1
†$p < .06$, *$p < .05$, **$p < .01$

Mediation Analysis

Data analyses were performed using the PROCESS macro (Hayes, 2018) for SPSS 23.0, and began with a simple mediation analysis using model 4. The first mediation analysis examining the mediating effect of reward sensitivity (PEP reactivity to reward) between stress and anhedonia symptoms controlled for the nonanhedonia symptom cluster of depression[2]. The analysis yielded a non-significant overall mediating effect of PEP reactivity; however, the significance of the paths differed (see Table 3). The *a*-path of the mediation analysis showed no main effect of stress exposure on PEP reactivity ($p = .19$). The *b*-path indicated a positive correlation between PEP reactivity and anhedonia symptoms ($p = .04$) such that individuals with larger PEP decreases reported lower levels of anhedonia symptoms.

Table 3
Mediation Analyses

	Consequent					
	M (PEP reactivity)			Y (Anhedonia)		
Antecedent	Coeff.	*SE*	*p*	Coeff.	*SE*	*p*
X (Stress Exposure)	0.90	0.67	.186	-0.02	0.14	.875
M (PEP reactivity)				0.05	0.02	.035
NonAnhedonia	-0.29	0.43	.510	0.37	0.09	<.001
Constant	-5.03	2.91	.089	0.28	0.60	.643
	$R^2 = .03$			$R^2 = .30$		
	$F(2, 69) = 0.90$, $p = .413$			$F(3, 68) = 9.87$, $p < .001$		

	Effect	Boot SE	LLCI	ULCI
Indirect Effect	0.05	0.04	-0.20	0.15

Note. PEP = Pre-ejection Period.

[2] The initial analysis included baseline PEP as a covariate given its correlation with both PEP reactivity and anhedonia symptoms. However, baseline PEP was not significant in the model (all *p*'s > .193) and was therefore removed from this final and all subsequent analyses.

Moderated Mediation Analysis

The next analysis examined whether stress exposure moderated the effect of stress reactivity (RSA reactivity to stress) on reward responding (PEP reactivity) within this mediation analysis. To examine this hypothesis, RSA reactivity was introduced as a moderator on the *a*-path of the previous mediation analysis. The initial model included baseline RSA and nonahedonia symptoms as covariates on both paths of the moderated mediation analysis. The initial analysis revealed that baseline RSA was not associated with PEP reactivity or anhedonia (both *p*'s > .48) and nonanhedonia symptoms did not predict PEP reactivity ($p = .65$). To improve overall model fit, I trimmed these non-significant variables from the final model. Specifically, I removed baseline RSA as a covariate on both paths and nonahedonia symptoms as a predictor on the *a*-path, which resulted in only nonanhedonia symptoms being controlled for on the *b*-path.

The final analysis of moderated mediation supported the hypothesis with the *a*-path interaction nearing significance ($p = .05$) and the *b*-path remaining significant ($p = .04$). As expected, stress predicted smaller PEP reactivity to reward for youth with the largest decreases in RSA to stress (see Table 4). Specifically, for youth with RSA withdrawal change scores of -0.86 (-0.50 SD below mean) and lower, exposure to stress significantly predicted PEP reactivity to reward (see Table 5 for Johnson-Neyman output; see Figure 2). In turn, youth with smaller PEP reactivity reported greater anhedonia symptoms.

Table 4
Moderated Mediation Analyses

		Consequent					
		M (PEPr)				Y (Anhedonia)	
Antecedent		Coeff.	*SE*	*p*		Coeff.	*SE*	*p*
X (Stress Exposure)	a_1	-0.48	0.79	.542	c'_1	-0.02	0.14	.875
W (RSAr)		10.07	5.18	.056				
Inter (RSAr x Stress)		-2.17	1.09	.051				
M (PEPr)					b	0.05	0.02	.035
NonAnhedonia					c'_3	0.37	0.09	<.001
Constant	i_1	0.80	3.67	.829	i_1	0.28	0.60	.643
		R^2 = .07				R^2 = .30		
		$F(3, 68) = 0.90$, $p = .156$				$F(3, 68) = 9.87$, $p < .001$		

	Index	Boot SE	LLCI	ULCI
Index of Moderated Mediation	-0.11	0.07	-0.27	-0.01

Note. PEP = Pre-ejection Period; RSA = Respiratory Sinus Arrhythmia; r = reactivity.

Table 5
Johnson-Neyman conditional effects

RSAc Level	Effect	LLCI	ULCI
-2.4713	4.8769	0.4608	9.2930
-2.3097	4.5264	0.4500	8.6028
-2.1481	4.1759	0.4369	7.9149
-1.9865	3.8254	0.4208	7.2299
-1.8249	3.4749	0.4008	6.5489
-1.6633	3.1243	0.3754	5.8733
-1.5017	2.7738	0.3425	5.2052
-1.3401	2.4233	0.2987	4.5480
-1.1785	2.0728	0.2385	3.9071
-1.0169	1.7223	0.1528	3.2918
-0.8553	1.3718	0.0265	2.7171
-0.8284	1.3134	0.0000	2.6268
-0.6937	1.0213	-0.1637	2.2064
-0.5321	0.6708	-0.4458	1.7874
-0.3705	0.3203	-0.8360	1.4767
-0.2089	-0.0302	-1.3246	1.2642
-0.0473	-0.3807	-1.8846	1.1232
0.1143	-0.7312	-2.4907	1.0283
0.2759	-1.0817	-3.1258	0.9623
0.4375	-1.4322	-3.7792	0.9147
0.5991	-1.7827	-4.4447	0.8793
0.7607	-2.1332	-5.1186	0.8521

Note. RSAc = Respiratory sinus arrhythmia change score; LLCI = Lower level confidence interval; ULCI = Upper level confidence interval

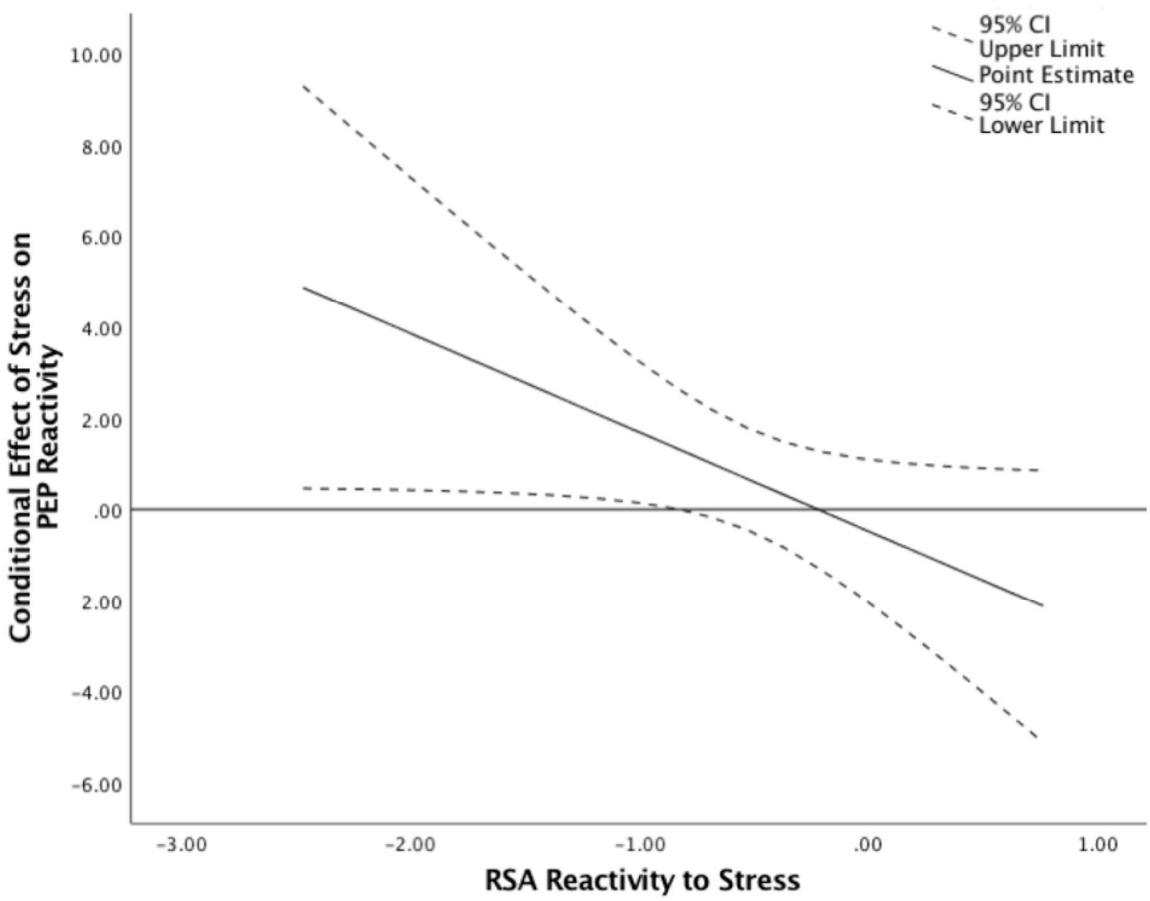

Figure 2. Conditional effect of stress exposure on PEP reactivity to reward as a function of RSA reactivity to stress.

To further examine and visualize the interaction effect, I performed a median split on the stress variable to reflect youth exposed to higher (N = 37) versus lower stress (N = 35). In addition, I performed a tertile split on the RSA reactivity variable such that youth were classified as having minimal/no withdrawal (RSAc = [0.76] – [-0.24]; N = 24), moderate withdrawal (RSAc = [-0.33] – [-0.74]; N = 24), and a large withdrawal (RSAc = [-0.78] – [-2.47]; N = 24). PEP reactivity to reward was then graphed as a function of the interaction between these categorical variables (see Figure 3). Although the ANOVA interaction term was not significant, the graphical presentation revealed a pattern of diminished PEP reactivity to reward among individuals reporting higher levels of stress

exposure. This suggests the differential impact of stress exposure is particularly affecting those with the largest stress response (RSA reactivity). That is, individuals who exhibited large physiological responses to stress and who were exposed to higher levels of stress display attenuated PEP reactivity to reward. In contrast, similarly large stress responders who are exposed to low levels of stress demonstrated normal PEP responses to reward. Interestingly, individuals who showed minimal to no stress response displayed similarly diminished PEP reactivity regardless of their exposure to stress.

After separating participants into these categories, I examined group-based differences on the dependent variable. An independent samples *t*-test was performed to examine group differences in PEP reactivity to reward in the lower versus higher stress exposed youth. This analysis indicated a significant difference (t [70] = -2.37, p = .02) such that youth exposed to lower levels of stress exhibited larger PEP decreases (M = -1.98, SE = 0.52) compared to those experiencing higher levels of stress (M = -0.34, SE = 0.45; see figure 4). I then performed a univariate analysis of variance (ANOVA) to examine the interaction and graph the interaction between the variables. The model summary can be found in Table 6. Of note, the ANOVA predicted a significant main effect of stress exposure on PEP reactivity such that higher stress was associated with a diminished PEP response to reward (b = .29; t = 2.45; p = .02). The main effect for RSA reactivity was not significant (b = .08; t = 0.68; p = .50). The interaction term was not significant (p = .11).

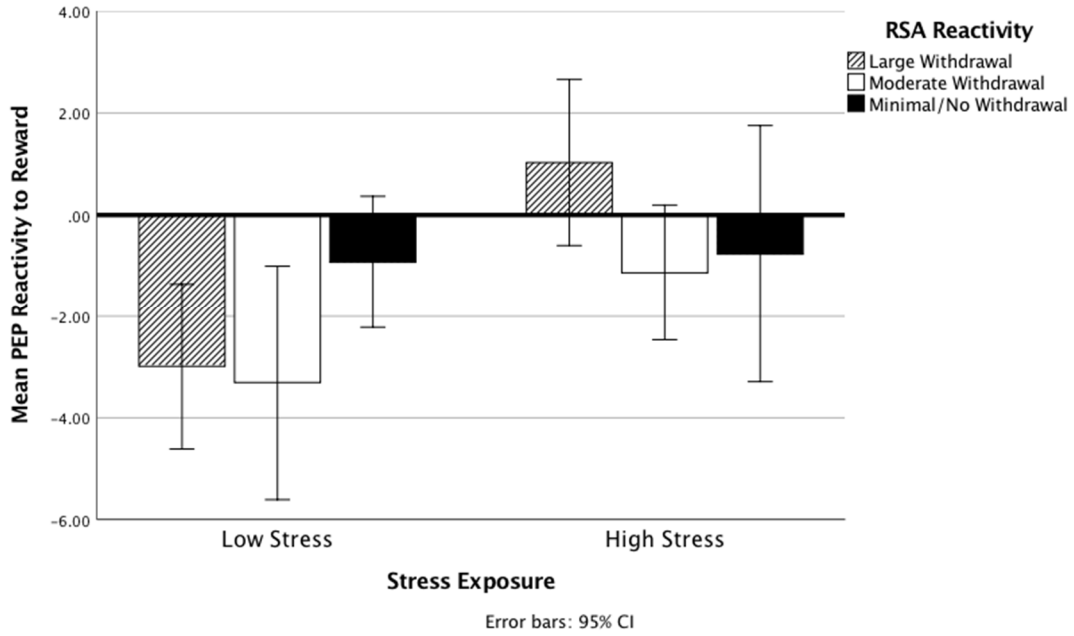

Figure 3. Graphical depiction of PEP reactivity to reward as a function of stress exposure and RSA reactivity to stress.

Figure 4. Mean PEP reactivity to reward as a function of stress exposure.

Table 6
Means, Standard Errors, and ANOVA Statistics for Stress Exposure by RSA Reactivity Predicting PEP reactivity

Predictor	*F*	*p*-value
Intercept	12.80	.001
Stress	7.87	.007
RSAc	1.31	.276
Stress X RSAc	2.24	.114

	Stress Exposure			Main Effect	
RSA Reactivity	Low (*SE*)	High (*SE*)	Diff.	*F*	*p*-value
No/Minimal Withdrawal	-0.93 (0.65)	-0.77 (1.26)	-0.16	0.01	.911
Moderate Withdrawal	-3.31 (1.15)	-1.13 (0.66)	-2.17	2.66	.108
Large Withdrawal	-2.99 (0.82)	1.03 (0.82)	-4.01	12.12	.001

Note. PEP = Pre-ejection Period; RSA = Respiratory Sinus Arrhythmia; r = reactivity.

CHAPTER IV

Discussion

Theoretical advancements in the understanding and conceptualization of depression highlight the need to assess specific symptoms and the etiological processes involved in their emergence (Chen et al., 2000; Fried & Nesse, 2015; Goldberg, 2011; Shankman & Gorka, 2015). Anhedonia is one such symptom with a recent theoretical update regarding its etiology (Pizzagalli, 2014), specifically identifying the pathophysiological relationship between greater stress exposure and suppressed dopaminergic reward responding. While this has accumulated strong support within animal models, there are comparatively less studies examining this relationship in humans. The current study aimed to address this gap using peripheral physiological indices of reward sensitivity, and to further evaluate the impact of physiological vulnerability on this relationship.

The results of this study provide preliminary support for the deleterious effects of stress on physiological reward responding, and it further provides clues about moderators of the stress and reward sensitivity relationship. First, while there is accumulating evidence of the sensitivity of PEP reward reactivity and depression (Ahles, Mezulis, & Crowell, 2017; Franzen & Brinkman, 2015; Silvia, Nusbaum, Eddington, Beaty, & Kwapil, 2014), no studies have examined precursors or developmental pathways to diminished PEP reactivity to reward. Thus, this study broadens and extends the effort-deficit literature of PEP by examining a mechanistic pathway through which stress impacts this central symptom of the depressive syndrome. Second, the vulnerability-stress model of depression underscores the role of individual differences in conferring

risk for the development of depression under conditions of stress (Hankin, 2012). The current study builds on this literature by examining differences in physiological stress reactivity in environmental contexts of higher and lower stress to predict the emergence of a specific symptom of depression (i.e. anhedonia). In the next few sections, I will review the results of the current study in the context of the broader literature.

Does PEP reactivity mediate the relationship between stress and anhedonia?

I hypothesized that the relationship between stress and anhedonia would be mediated by PEP reactivity to reward tasks. More specifically, I expected that higher levels of reported stress exposure would correlate with more diminished PEP reactivity in response to a reward task. Consistent with previous studies, I then anticipated that diminished PEP reactivity would be associated with greater self-reported anhedonic symptoms.

The proposed and post hoc analyses revealed a complex set of findings, which point to general support for the first set of hypotheses. The results of the bivariate and initial mediation analysis found no relationship between stress and PEP reactivity. However, when stress exposure was dichotomized into higher and lower levels, there was a clear difference such that youth exposed to higher stress exhibited significantly diminished PEP reactivity to the reward task compared to their lower stress counterparts. Similar to previous findings (e.g. Silvia et al., 2014), the relationship between diminished PEP reactivity to reward and greater anhedonia symptoms was supported.

The results of this first hypothesis are consistent with the heuristic model of stress impacting reward sensitivity (Pizzagalli, 2014) as well as with the theory of allostatic load (McEwen, 2008). According to this model, prolonged exposure to stress is

associated with downregulation of mesolimbic dopamine pathways, a key substrate involved in incentive motivation. Importantly, this relationship appears to be specific to chronic unavoidable stressors, fitting with learned helplessness models of depression. The allostatic load model addresses changes in physiological functioning as arising from the concept of allostasis (Goldstein & McEwen, 2002). Allostasis refers to shifts in set points within biological systems such as stress and reward responses due to the influence of environmental stress (Beauchaine, Neuhaus, Zalewski, Crowell, & Potapova, 2011; Hinnant, El-Sheikh, Keiley, & Buckhalt, 2013). In turn, alterations in these set points may lead to overload "wear and tear" from either overexposure to chronic stress or to poor management of stress/reward responses leading to pathological behavioral and physiological outcomes (Beauchaine et al., 2011; McEwen, 2008). In the current study, allostatic shifts in physiological reward responding due to higher levels of stress exposure may have contributed to anhedonic symptoms.

Does physiological stress reactivity moderate the relationship between stress and reward sensitivity?

I hypothesized that the relationship between stress and PEP reactivity would be moderated by physiological stress reactivity as measured by RSA reactivity to a lab stressor. Greater RSA reactivity to negative affect inductions is associated with greater internalizing symptoms and it may be this greater physiological arousal leads to more intense emotional experience (Fortunato, Gatzke-Kopp, & Ram, 2013). This exaggerated physiological response may intensify the impact of stress on reward functioning resulting in a more profound impact of stress on reward responding. Consistent with my previous

hypothesis, I expected those with the more diminished PEP reactivity to report greater anhedonia symptoms.

This study supported the hypothesis that individuals with large RSA withdrawal to a lab stressor task would show smaller PEP reactivity to reward if exposed to higher levels of stress during the previous six months. In contrast, similarly strong RSA withdrawing youth exposed to lower amounts of stress displayed larger PEP reactivity to reward. However, further investigation of this interaction revealed a pattern that, on average, youth exposed to higher levels of stress displayed similarly diminished PEP reactivity regardless of RSA reactivity (see figure 4). For youth exposed to lower levels of stress, PEP reactivity remained similarly robust for both high and moderate RSA withdrawers. In contrast, a trend was observed suggesting youth with minimal/no RSA withdrawal had smaller PEP responses to reward than those with moderate to high RSA withdrawal.

While acknowledging the limited power and marginal trend toward significance, the proposed and post hoc analyses of this hypothesis may offer some clarification to the RSA reactivity literature. Moderate RSA reactivity to stress is hypothesized to be a marker of resilience in contexts of stress and adversity (Zisner & Beauchaine, 2016a), and the results are mixed regarding blunted or exaggerated RSA withdrawal being associated with internalizing problems (Graziano & Derefinko, 2013).

Some research suggests that exaggerated RSA reactivity is associated with internalizing problems (Zisner & Beauchaine, 2016a) and suggests poor capacity for self-regulation. For these individuals, especially when paired with lower baseline RSA levels, this excessive reactivity may lead to the physiological dysregulation similar to panic and

anxiety (Hinnant & El-Sheikh, 2013). It may be that in a context of low exposure to stress, these individuals do not accrue the same overload as when they are exposed to higher and/or more chronic stress (McEwen, 2008). This differential effect was found in the current study, which suggests that mixed findings for excessive RSA reactivity to stress and internalizing symptoms may partly depend on the context of stress the individual is experiencing.

On the other hand, the finding of no/minimal stress responders displaying similarly diminished PEP reactivity regardless of stress exposure reflects another common finding indicating blunted RSA reactivity to stress as associated with internalizing problems (Schmitz, Krämer, Tuschen-Caffier, Heinrichs, & Blechert, 2011). This pattern of responding may be best understood as indicating "autonomic inflexibility" (Hoehn-Saric, & McLeod, 2000; Lyonfields, Borkovec, & Thayer, 1995). As discussed in the introduction, physiological flexibility, responsivity, and adaptation to stressors and environmental demands promotes adaptive cognitive and behavioral responses (Porges, 2007; Thayer & Lane, 2000). Autonomic inflexibility is characterized by a lack of dynamical physiological adjustment to circumstances and may be indicative of a reliance on avoidance and worry to manage stressful situations as seen in phobia (Schmitz et al., 2011) and generalized anxiety disorder (Lyonfields et al., 1995; Seeley, Mennin, Aldao, McLaughlin, Rottenberg, & Fresco, 2016). Given the high comorbidity (Garber & Weersing, 2010) and overlapping perseverative cognitive regulation strategies between anxiety disorders and depression (Aldao, Nolen-Hoeksema, & Schweizer, 2010), it may be that youth in this study are exhibiting a similar autonomic rigidity.

The presence of this rigidity makes for more complex discussion about the time-course of symptom emergence in youth with these profiles. That is, to what extent might alterations in the stress reactivity be a product of allostatic processes (McEwen, 2008)? There is evidence to suggest that individuals exposed to chronic stress display lower levels of baseline RSA as well as RSA reactivity (Daches et al., 2017; El-Sheikh & Hinnant, 2011; Hinnant et al., 2013; McLaughlin, Sheridan, Tibu, Fox, Zeanah, & Nelson III, 2015). Following from both the law of initial values and evidence of attenuated reactivity among those with psychopathology (Ginty, 2013; Lyonfields et al., 1995), it may be that youth in this study who exhibit minimal/no RSA reactivity are displaying the impacts of years of chronic stress and therefore demonstrate autonomic inflexibility in both RSA reactivity as well as PEP reactivity, indicating an overall biological disengagement (Ginty, 2013). Clearly, more research is required to adequately classify the differences between responders as well as assess the stability in physiological responses across development.

A final consideration regarding the interplay between stress, RSA reactivity, PEP reactivity, and depressive symptoms is heterotypic comorbidity (Angold, Costello, & Erkanli, 1999) and the stress generation hypothesis of depression (Hammen, 2006). First, heterotypic comorbidity in psychology refers to the presence of multiple disorders occurring in different diagnostic groupings (e.g. at least one internalizing and one externalizing disorder; Angold et al., 1999). Although correlations are higher within each diagnostic grouping (e.g. anxiety and depression correlate higher than depression and conduct disorder), epidemiological work clearly indicates a high level of heterotypic comorbidity (Zisner & Beauchaine, 2016b). Moreover, there appear to be temporal

patterns such that externalizing problems in childhood predict later depressive symptoms (Loth, Drabick, Leibenluft, & Hulvershorn, 2014). It may be that individuals at risk or currently engaging in externalizing behaviors generate stress within their environment, which may in turn feedback on their mood. This would be consistent with work suggesting depressed and at-risk individuals – including nondepressive disorders - generate greater levels of depressogenic stress (see Liu & Alloy, 2010). Furthermore, there is accumulating evidence of shared neural substrates between externalizing disorders and depression, which include low mesolimbic dopamine responding to reward (Zisner & Beauchaine, 2016b). Given the association between blunted RSA stress responding and externalizing symptoms (Graziano & Derefinko, 2013) as well as the highly replicated relationship between attenuated PEP reactivity to reward and externalizing problems (for review, see Zisner & Beauchaine, 2016a), it may be that these youth generated more stress in their life or had pre-existing trait-like deficiencies in these markers. Once again, future research can help to resolve these outstanding questions via longitudinal studies assessing physiological responses at multiple time points and characterizing the contexts of stress in which they are embedded.

Clinical Application

The current study helps add and clarify a symptom-specific pathway for the emergence of anhedonic features, which may help clinicians conceptualize and treat depression in adolescence. This study indicated that those exposed to higher levels of stress showed blunted physiological reward sensitivity, which in turn was associated with more reported anhedonic symptoms. While further research is needed to determine the extent to which stress causally impacts PEP reactivity to reward, there are theoretical

approaches and empirical findings that address reward/motivation deficits associated with depression. Behavioral activation therapy is an evidence-based treatment for depression focusing on increasing exposure to rewarding stimuli and reducing avoidance (McCauley, Schloredt, Gudmundsen, Martell, & Dimidjian, 2016). One study examining the impact of behavioral activation therapy for depressed adults found functional changes in reward-related structures in the brain (Dichter, Felder, Petty, Bizzell, Ernst, & Smoski, 2009), which by extension would suggest decreases in anhedonia. On the other hand, some research has found persistent deficits in reward responsiveness among those with remitted depression (Pechtel, Dutra, Goetz, & Pizzagalli, 2013; Weinberg & Shankman, 2017). This again highlights the need to understand the degree to which blunted reward responding emerges as a consequence of stress, is a trait-like vulnerability, or if it is a scarring effect (Burcusa & Iacono, 2007).

This study also showed that individuals with exaggerated RSA withdrawal to stress showed more maladaptive PEP reward reactivity under conditions of higher stress. Some researchers have speculated that greater RSA withdrawal to negatively valenced tasks may indicate heightened attentional engagement with the stimuli, thereby decreasing emotion regulation and intensifying the experience (Fortunato et al., 2013; Hinnant & El-Sheikh, 2009; Thayer & Lane, 2000). For these individuals, it may be useful to target broad emotion regulation strategies as well as to help modulate their attentional control (Joorman & Stanton, 2016; Koster, De Lissnyder, Derakshan, & De Raedt, 2011).

Limitations and Future Directions

Several limitations of the current study should be acknowledged. First, there are several ways in which our characterization of stress could improve. Our measure of stress was a checklist, and this method of assessing experience has received many critical reviews (Dohrenwend, 2006). For one, it is often hard to disentangle influences such as participants' subjective impressions of an event as negative as well as the confounding between some events and psychopathology (Hankin, Abramson, & Siler, 2001). While some have reconstructed checklists to reflect "objective stressors" (Hankin et al., 2001), there are likely differences in the experience of these events as stressful that cannot be assessed by self-reported weighting of stress. In addition, while many stressful events are common to most people, there may be instances in which one experiences an event not included in the checklist.

Although more time-intensive, semistructured interviews such as the Life Stress Interview (Rudolph & Hammen, 1999) involve interviews of both parent and youth to assess stressful experiences across several areas of the child's life. Following this, trained researchers code the information in terms of domain, chronicity, and severity. This may have important implications for the study of reward sensitivity given the centrality of chronic stress in the models of anhedonia and pathological reward functioning (Beauchaine et al., 2011; Pizzagalli, 2014). In addition, stress can differ in its degree to which the event is dependent or independent of the individual's actions, characteristics, or mood. Another salient domain, particularly in adolescence, is whether an event is interpersonal or noninterpersonal (Ahles, Harding, Mezulis, & Hudson, 2015). These different domains of stress have varying associations with depressive symptoms,

and parsing them out may help illuminate even greater specificity in the relationship between stress and anhedonia symptoms.

A second limitation to the current study is the restriction for study inclusion, which means that our sample does not reflect youth with psychopathology. This has an influence on both the generalizability to depressive disorders as well as the variability among the predictor variables. Beauchaine (2009) cautions against the generalization of physiological profiles from developmental samples to clinical samples noting that differences in the mechanisms predicting behavior may differ at the extremes of a distribution. By screening out children elevated in depressive symptoms, we clearly reduced variability in depression but likely also reduced the variability in other measures of vulnerability such as RSA reactivity to stress.

In addition to the restriction of variability associated with pathology, there is also a question of specificity and validity in our laboratory stressor. Although unsolvable anagrams reliably elicit affective and physiological changes (Smith, 1996; Weidner, Friend, Ficarrotto, & Mendell, 1989), researchers in RSA reactivity have called for greater refinement in stimulus selection to make greater inferences about the specific affective state of the participant (Fortunato et al., 2013; Zisner & Beauchaine, 2016a). While our stressor task on average generated RSA withdrawal, it may be that our participants experienced any number of reactions including fear, frustration, challenge, confusion, or annoyance. To some extent, these different responses are going to be mediated by cognitive processes and therefore may be valuable indicators of risk. At the same time, this potential heterogeneity in responses makes it increasingly difficult to draw conclusions about the state of the individual during the task. In contrast, specific

emotion inductions (e.g. see Fortunato et al., 2013) are likely to refine the interpretations about motivational or affective states.

Limitations considered, this study contributes to the growing literature examining stress and reward functioning. While future research will benefit from incorporating changes outlined above, the recurring theme throughout the discussion section is the need to establish better temporal relationships among these constructs. Specifically, it would be helpful to assess PEP reactivity to reward and RSA reactivity to emotion evocation at multiple time points across development. Such a design would provide premorbid indicators of physiological functioning and help build causal arguments for the role of stress. In addition, this may shed light on diminished PEP reactivity to reward as a trait vulnerability, a state response to stress, or potentially an equifinal biomarker subject to both genetic and environmental determinants. It may also be interesting to examine the recovery of PEP reward responding either in the face of stress or after it subsides. That is, do interventions such as behavioral activation and emotion regulation training reactivate a potentially stress-suppressed PEP reactivity? An additional area for future research is to assess the sensitivity of PEP reactivity to reward to acute lab stressors within the same visit given the research linking acute bouts of stress with impaired reward processing (Bogdan & Pizzagalli, 2006).

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