PHYSIOLOGICAL MARKERS OF STRESS GENERATION AND AFFECT REACTIVITY IN DEPRESSION

A Dissertation
Submitted to the
Temple University Graduate Board

In Partial Fulfillment
of the Requirements for the Degree
DOCTOR OF PHILOSOPHY

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August 2017

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ABSTRACT

Although existing research has evaluated physiological and environmental risk factors for depression, these processes are often examined in isolation without considering the dynamic relationships in risk for depression. The present study evaluated physiological markers of resting and stress-reactive respiratory sinus arrhythmia (RSA and RSA reactivity) as predictors of depressive symptoms and interpersonal stress generation, a mutable and potent vulnerability for depression. Further, we examined whether stress generation predicted subsequent depressive symptoms. In a sample of late adolescents (N = 105; 18-22 years; 76% female), individuals who screened in for a history of clinical and subclinical depression participated in a micro-longitudinal assessment with a diagnostic interview, in-laboratory socio-evaluative stressor task, and two weeks of daily assessments of stressful events and depressive symptoms. First, results indicated that there were no clinical or physiological differences between individuals with a clinical or subclinical depression history. Our multilevel modeling analyses revealed that: 1) only lower levels of resting RSA predicted depressive symptoms over the two-week period; 2) only lower RSA reactivity predicted greater interpersonal stress generation, but not independent stressors; 3) interpersonal stress generation mediated the relationship between RSA reactivity and depressive symptoms, but not resting RSA and depressive symptoms; 4) sex differences only occurred in the relationship between resting RSA and depressive symptoms; and 5) there were no interactive effects of resting RSA and RSA reactivity on depression or interpersonal stress generation. These findings highlight the importance of assessing both resting RSA and RSA reactivity in the examination of depression and depression-related processes.

This dissertation is dedicated to:

My parents, Debbie and Charlie, whose love and support know no bounds;

my sister, Kristen, for being an inspiring teacher for her students and me;

my niece, Summer, for bringing out my inner child every time we're together;

and my partner, Jordan, for being someone I can learn from and laugh with,

and who makes every day better just by being there;

All of your love, support, and encouragement made this possible.

ACKNOWLEDGEMENTS

First and foremost, I would like to thank my mentor, Dr. Lauren B. Alloy. Lauren, thank you so much for all of your support and guidance over the past five years. You have been gone above and beyond to provide countless opportunities to further my career as a clinical scientist. You have taught me so much over the past five years, including how to conduct high-impact, high-quality research, and how to be an amazing teacher and mentor. I am so fortunate to have the opportunity to join your impressive academic family tree, and only hope that I can make you proud in the future.

I also would like to thank Dr. Thomas Olino for his generosity with his time and statistical knowledge, which has been crucial in my career development and for this dissertation. I am honored to follow in your footsteps for internship. I also need to extend thanks and gratitude to the other members of my dissertation committee, Drs. Deborah Drabick, Philip Kendall, Tania Giovannetti, and Kareem Johnson. I have had the tremendous opportunity to know each of you as teachers, researchers, and clinicians. My graduate school experience has been rich and memorable thanks to all of you. I must also thank the National Institute of Mental Health for providing me with a National Research Service Award, which funded this project and provided generous support for my tuition and other professional activities over the past two years.

I also would like to acknowledge the Mood and Cognition Lab, who have been my collaborators and friends throughout graduate school. They have been there with me through it all and made my nights and weekends in lab much brighter with your kindness and friendship. In particular, thank you to Jonathan Stange for being a collaborator, mentor, and friend that I greatly admire, Taylor Burke for her support and collaboration,

and Samantha Connolly for being the best officemate and partner through every step of the program. I would especially like to thank the members of the Stress and Emotion Study Team, without whom this dissertation would not be possible. Thank you to Kate, Morgan, and Joe for your hard work and for helping me run participants, and especially Andrew Gepty, who has been my right arm through all of this. I am so thankful to have worked alongside such an incredible team. I owe a special thanks to my cohort. You are the most generous, kind, intelligent, and talented individuals and I am so fortunate to have grown alongside each and every one of you.

Thank you so much to all of the faculty, friends, and family, who have supported and inspired me for the past five years and beyond. I would like to thank my family, Debbie and Charlie, who have devoted their lives to making me and Kristen (and now Summer) into strong and successful women. Thank you both for everything you have sacrificed to help me become the person I am today. Finally, I would like to thank my partner, Jordan. Jordan, you are my other half and I share this success with you. Thank you for being there for me in every way imaginable and helping me achieve my dreams.

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CHAPTER 1

MANUSCRIPT IN JOURNAL ARTICLE FORM

Depression is a severe and debilitating disorder, which is associated with considerable costs at both the individual and societal levels (Greenberg, Fournier, Sisitsky, Pike, & Kessler, 2015; Kessler et al., 2009). Beyond major depression, subthreshold depression is associated with a course and impairment similar to clinical depression (Gotlib, Lewinsohn, & Seeley, 1995; Kessler, Zhao, Blazer, & Swartz, 1997), and is predictive of the first onset of a major depressive episode (van Lang, Ferdinand, & Verhulst, 2007). Part of depression's debilitating effect is due to its high rates of recurrence, with approximately 50% of individuals who recover from a depressive episode likely to have another episode in their lifetime (American Psychiatric Association, 2000), and up to 80% of those with a history of two or more episodes of depression having a recurrence (Burcusa & Iacono, 2007). Although there are a number of risk factors for depression, stressful events are considered to be among the most robust predictors of depression onset and recurrence (Burcusa & Iacono, 2007; Kendler, Karkowski, & Prescott, 1999; Monroe, Slavich, & Georgiadas, 2014, for a review). To better understand the role of stress in depression, it is important to clarify the dynamic relationship between two important stress-related processes: the psychophysiological stress response and stress generation.

Psychophysiological Reactivity and Depression

When an individual experiences stress, the Autonomic Nervous System (ANS) coordinates the mobilization of resources through dynamic interactions of the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) to

produce various degrees of physiological arousal. According to research and theory, the brain receives input regarding the internal and external environment and adjusts physiological arousal by transmitting output to the sinoatrial node of the heart, the heart's primary "pace maker" (Appelhans & Luecken, 2008; Berntson et al., 1997). The interplay of SNS and PNS neural activity in regulating the variation in time intervals between heartbeats is the basis of heart rate variability (HRV). Thus, HRV reflects the brain's sympathetic and parasympathetic control of the heart (Porges, 2007; Thayer & Lane, 2000). Specifically, SNS activity is associated with excitatory influences on the heart and results in acceleration of heart rate, which is reflected in shorter time between heartbeats. In contrast, PNS activity inhibits the sinoatrial node and contributes to heart rate deceleration, indexed by longer intervals between heartbeats. In this sense, HRV is a complex process and reflects the capacity of the brain and body to respond (*resting levels*) and the extent to which they can flexibly adapt to environmental challenges (*reactivity*; Porges, 1995; 2003a; 2007; Thayer & Lane, 2000), with HRV *reactivity* operationalized as changes in HRV levels during stress compared to rest.

A marker of HRV that has garnered significant attention in the depression literature is respiratory sinus arrhythmia (RSA), which is HRV that occurs in the high-frequency range of respiration (HF-HRV; hereafter referred to as RSA) and is reflective of PNS control over the heart. Specifically, it has been theorized that the PNS exerts its influence on the heart via the vagus nerve (i.e., tenth cranial nerve) and acts as a vagal "brake" to inhibit heart rate and sympathetic activation (Porges et al., 2007). Thus, higher levels of resting RSA reflect a greater capacity to apply the vagal "brake" and self-regulate (Beauchaine, 2001; Porges, 2007). Consistent with this, research indicates that

higher resting levels of RSA reflect more cognitive and attentional control, whereas lower resting RSA levels are associated with poorer emotion regulation and executive functioning (Appelhans & Luecken, 2006; Hansen, Johnsen, & Thayer, 2003; Thayer & Brosschot, 2005). Further, recent meta-analyses indicate that lower levels of RSA are consistently demonstrated among children, adolescents, and adults with current and past depression (for meta-analytic reviews, see Kemp et al., 2010; Koenig et al., 2016; Rottenberg, 2007).

In response to environmental challenges or stress, the vagal "brake" is typically released, thereby decreasing control of the heart via the vagus nerve. Release of the vagal "brake" also facilitates the activation of the SNS when confronted with stress to mobilize physiological and cognitive resources to effectively manage and cope with stress. In this sense, greater physiological reactivity to stress (e.g., more RSA reactivity) is generally considered to be an adaptive response to stress, whereas *blunted RSA reactivity* is indicative of less efficient responses to stressors (Porges, 1995, 2003a, 2007; Rottenberg, 2007). Although RSA is not a direct index of vagal tone (Berntson, Cacioppo, & Quigley, 1993), research indicates that resting RSA levels and RSA reactivity may serve as important indices of the ability to self-regulate and *react* to stress in the environment (Porges, 2007; Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012).

Surprisingly, few studies have focused on RSA reactivity to psychosocial stressors, such as speeches, mental arithmetic tasks, or sad films. These studies consistently document that individuals with current depression exhibit *blunted* RSA reactivity to laboratory stressors (e.g., Bylsma, Salomon, Taylor-Clift, Morris, & Rottenberg, 2014; Rottenberg, Clift, Bolden, & Salomon, 2007). However, studies of past

depression yield mixed findings, with some studies finding that adults with past depression also exhibit blunted RSA reactivity (e.g., Yaroslavsky, Bylsma, Rottenberg, & Kovacs, 2013; Yaroslavsky, Rottenberg, & Kovacs, 2014), whereas others suggest that adults with remitted depression exhibit similar reactivity to healthy controls (e.g., Bylsma et al., 2014). Importantly, recent research has demonstrated the importance of assessing the combined influence of resting RSA and reactivity by examining their interactive effects (Yaroslavsky, Rottenberg, et al., 2013; 2014). These studies find that atypical RSA patterns, such as lower resting RSA and greater withdrawal, increase the risk of depression, whereas more adaptive patterns include higher resting RSA and greater RSA withdrawal, which predict reduced risk of depression.

Limits to our Understanding of RSA and Depression

Although these studies have provided valuable information about the relationship between RSA and depression, our understanding of resting RSA and RSA reactivity is still in its early stages. For instance, relatively few studies have examined potential sex differences in the association between RSA and depression, largely because of small sample sizes or an all-female sample. Several studies have observed sex differences in resting RSA (Chambers & Allen, 2007; Thayer, Smith, Rossy, Sollers, & Friedman, 1998), finding that depressed women generally have higher resting levels of RSA than men (Chambers & Allen, 2007; Thayer et al., 1998). Interestingly, two studies of RSA reactivity obtained differing patterns, with one finding that men had less RSA reactivity to a speech stressor in a community sample of relatively healthy men and women (Hughes & Stoney, 2000), whereas women experienced less RSA withdrawal to an emotion-induction than men in a sample of healthy adults and adults with juvenile-onset

depression (Yaroslavsky, Rottenberg, et al., 2013). Further, some studies of RSA reactivity and depressive symptoms have not observed sex differences in these processes (Gordon, Ditto, & D'Antono, 2012; Matthews, Nelesen, & Dimsdale, 2005). One possibility for these discrepant findings may be differences in the sample included, such as those with depressive history versus community samples, or the type of task used to induce stress (e.g., emotion versus socio-evaluative). Importantly, these studies have focused on adults, whereas studies of youth have demonstrated more sex differences in RSA levels and reactivity. However, future research is needed to evaluate potential sex differences that may exist in the physiological predictors of depression.

In addition, most existing research on RSA, particularly RSA reactivity, has compared individuals with and without major depression (current or past). However, given research indicating that both major and subclinical depression confers significant impairment for affected individuals (Kessler et al., 1997), it is possible that individuals with subclinical depression may exhibit similar physiological patterns as those with clinical depression. However, no known research has examined individuals with current or past clinical and subclinical depression. In addition, by only examining group differences of those with and without (current or past) depression, these studies do not take into account the significant heterogeneity that exists within depression (Goldberg, 2011), which may differentially influence (and be influenced by) physiological processes. Specifically, when group differences between people with and without depression are examined, it remains unclear whether there are individual (within-group) differences in resting RSA levels or reactivity among those with current or past depression. . Better understanding whether the effects of RSA are specific to major depression or also are

characteristic of subclinical depression, as well as whether there are within-group differences in the effects of RSA on depression may elucidate the relationship between depression and RSA.

Finally, another notable limitation is the dearth of studies utilizing a longitudinal design to examine the effects of RSA on depression. Most studies have examined group differences in resting RSA and RSA reactivity associated with depression during one laboratory session, but have not examined whether resting RSA or RSA reactivity prospectively predicts depressive symptoms or episodes, particularly among those known to be at risk because they had prior depression. Importantly, more recent studies have investigated resting RSA and reactivity as prospective predictors of depression recovery, finding evidence that greater RSA reactivity/withdrawal predicted recovery from depression and fewer prospective depressive symptoms (Panaite et al., 2016; Rottenberg, Salomon, Gross, & Gotlib, 2005). In addition, studies of children and adolescents demonstrate that lower resting RSA levels predicted greater depressive symptoms one year later (Vazquez et al., 2016) and greater RSA reactivity predicted fewer prospective depressive symptoms among at-risk youth (Gentzler, Santucci, Kovacs, & Fox, 2009). In addition, adolescents with atypical RSA patterns (low resting RSA and greater RSA withdrawal/high resting RSA and RSA augmentation) were at increased risk for prospective depressive symptoms across adolescence (Yaroslavsky et al., 2014). However, no known study has examined resting RSA and reactivity as a prospective predictor of depressive symptoms among late adolescents/young adults, nor examined this relationship among individuals vulnerable to future depression by virtue of having had past depression. Simultaneously examining whether resting RSA and RSA reactivity

differs among those with clinical and subclinical depression history *and* prospectively predicts depressive symptoms would inform the field about whether atypical RSA patterns in resting state and reactivity are only scars of major depression or are also a contributor to future risk.

Stress Generation and Depression

Although lower RSA and blunted RSA reactivity have been documented in depression, less is known about the role of RSA in depression-related processes known to confer risk for the maintenance, recurrence, and onset of depression. Given that the occurrence of stress is necessary to demonstrate atypical RSA *reactivity*, it is noteworthy that individuals with current and remitted depression, as well as those at risk for depression, tend to encounter higher levels of stressful events in their lives, particularly in their interpersonal relationships (Liu, 2013). This stress generation effect, whereby individuals shape their interpersonal environments and directly or indirectly contribute to stressful events *dependent* on their characteristics or behaviors (Daley et al., 1997; Hammen, 1991; Hammen & Brennan, 2002), has received considerable support over the past two decades. In particular, research has demonstrated that individuals with current, past, or subthreshold depression (Clements, Aber, & Seidman, 2008; Davila, Hammen, Burge, Paley, & Daley, 1995; Hammen & Brennan, 2002; Hankin, Mermelstein, & Roesch, 2007; Liu & Alloy, 2010) generate negative events in their interpersonal relationships (hereafter referred to as *interpersonal dependent events*) that are at least in part dependent on them. However, this is specific to interpersonal dependent events and does not occur for events that are independent (i.e., fateful events to which we would not expect someone to contribute), such as parents' divorce or illness of a loved one.

Given these findings, research also has extended the examination of the stress generation process to vulnerability factors for depression to better understand *why* certain individuals at risk for depression may contribute to dependent events in their interpersonal relationships. These studies have found that individuals who possess certain vulnerabilities to depression, such as maladaptive cognitive and interpersonal styles (Eberhart & Hammen, 2009; Hamilton, Stange, Kleiman, et al., 2013; Hamilton, Stange, Shapero, et al., 2013; McLaughlin & Nolen-Hoeksema, 2012; Safford, Alloy, Abramson, & Crossfield, 2007), generate interpersonal dependent stressors beyond the effects of current depressed mood. Stress generation, in turn, is a robust predictor of first onset and recurrent depression (Liu, 2013). Specifically, the occurrence of stressful events is one of the best predictors of depression, including first onset (Kendler et al., 1999; Lewinsohn, Allen, Seeley, & Gotlib, 1999; Monroe, Rohde, Seeley, & Lewinsohn, 1999), relapse (Burcusa & Iacono, 2007; Monroe, Roberts, Kupfer, & Frank, 1996), and depressive symptoms (Ge, Lorenz, Conger, Elder, & Simons, 1994). However, there is also evidence of a "kindling" effect of stress, whereby less severe events or daily hassles precipitate depression onset among individuals with subthreshold or past history of depression (Monroe & Harkness, 2005; Stroud, Davila, & Moyer, 2008). Thus, identifying markers of interpersonal stress generation is critical for identifying individuals at heightened vulnerability to experience *interpersonal dependent* stressors, which is a potent and malleable risk factor for depression.

Physiological Reactivity and Stress Generation

Surprisingly, little research has moved beyond self-report indicators of stress generation, and no known study has evaluated physiological processes (e.g., RSA) known

to be associated with depression as predictors of stress generation. However, individual differences in resting RSA and RSA reactivity are generally considered to be markers of self-regulation and stress-regulation (Thayer & Lane, 2000; Thayer et al., 2012). Specifically, individuals with higher levels of resting RSA and who experience greater RSA withdrawal to stressors have the ability to flexibly respond to changing demands or modulate their emotional and behavioral responses, which facilitates effective coping strategies and more adaptive interpersonal behaviors (Porges, 2003a). Thus, it is possible that individuals with lower resting RSA and *blunted* RSA reactivity to stress may have more difficulty with self- and stress-regulation, thereby contributing to more negative events in their lives, particularly in their interpersonal relationships. Thus, atypical RSA patterns may result in maladaptive responses to stress, which, in turn, further contribute to the dysregulated physiological reactivity, resulting in a cyclical relationship for increased depression.

Although there has been no direct evidence to date for this hypothesis, some research has found that individuals with higher resting RSA and greater RSA withdrawal during a stressor task exhibit more adaptive emotional responses and interpersonal functioning (Porges, 2003a; 2003b; Yaroslavsky, Bylsma, et al., 2013). Relatedly, lower RSA and blunted RSA reactivity is associated with negative interpersonal behaviors (Porges, 2003b), including reduced interpersonal warmth (Diamond & Cribbet, 2013), poor social skills (Blair & Peters, 2003), and social disengagement (Geisler, Kubiak, Siewert, & Weber, 2013), as well as maladaptive cognitive strategies, such as emotional suppression and rumination (Thayer & Brosschot, 2005;Yaroslavsky, Bylsma, et al., 2013). In studies of stress generation, these negative behaviors have been found to predict

poor interpersonal relationships more generally, and specifically, interpersonal stress generation (Caldwell, Rudolph, Troop-Gordon, & Kim, 2004; McLaughlin & Nolen-Hoeksema, 2012; for a review, see Liu, 2013). Importantly, blunted RSA reactivity also is associated with neuroticism (Hughes, Howard, James, & Higgins, 2011; Jonassaint et al., 2009), which is a robust prospective predictor of stress generation over longer intervals (Uliaszek et al., 2010) and on a daily basis (Gunthert, Cohen, & Armeli, 1999). Although these studies lend indirect support, there is preliminary evidence that lower RSA reactivity actually predicted more daily negative interactions among couples, thereby suggesting that there is a relationship between blunted RSA reactivity and heightened daily stressors (Diamond, Hicks, & Otter-Henderson, 2011). Thus, it is possible that blunted physiological reactivity to stress would specifically predict the occurrence of more interpersonal *dependent* stressors, but not stressors that occurred independently of the individual. Although there is indirect support for this relationship, no study to date has evaluated resting RSA and RSA reactivity as a predictor of daily stress generation, which might provide more objective units of analysis as markers of risk for interpersonal stress generation and insight into a potent process that contributes to first onset and recurrence of depression.

The Current Study

Recent research points to the importance of assessing daily stressors to gain insight into the everyday processes that confer risk for depression at the level of analysis at which they unfold (aan het Rot, Hogenelst, & Schoevers, 2012). Thus, micro-longitudinal or daily study designs are well-suited to explore the idiographic and complex relationships that may exist. The primary aim of the present study was to evaluate

whether individual differences in RSA patterns predicted daily interpersonal stress generation and depressive symptoms among individuals with a history of depression (and therefore, at risk for subsequent depression). Specifically, we examined whether resting RSA, RSA reactivity, and the interactive effects of RSA resting and reactivity would predict higher levels of depressive symptoms and interpersonal *dependent* stressors, but not *independent* stressors, over two weeks of daily diary assessments. In addition, our second aim was to examine whether stress generation would mediate the relationship between RSA patterns and depressive symptoms. Finally, our exploratory aim was to examine potential sex differences in the relationship between RSA patterns and depression given research that women are at greater risk for both stress generation and depressive disorders (Hankin et al., 1998).

Given that lower levels of RSA and blunted RSA reactivity are associated with higher levels of daily stressors (Diamond et al., 2011), we hypothesized that lower RSA levels and blunted RSA reactivity would be associated with both greater depressive symptoms and daily interpersonal dependent stressors over the next two weeks. We also expected that this would be specific to interpersonal dependent stressors, but not independent stressors. Further, we also hypothesized that daily stress generation would serve as a mediator between lower RSA and blunted RSA reactivity and depressive symptoms in the micro-longitudinal assessments. In addition, although our hypotheses regarding sex differences were exploratory, we hypothesized that women with maladaptive or atypical RSA patterns (likely lower RSA levels and blunted RSA reactivity) would be at greater risk for both depressive symptoms and interpersonal stress generation.

Method

Recruitment

The current sample of 105 late adolescents (ages 18-22) was recruited as part of the Stress and Emotion Study at Temple University to evaluate the predictive association between physiological reactivity to a laboratory stressor task and the occurrence of stressful events and depressive symptoms among individuals with a history of subthreshold or clinical depression. Participants were recruited from the Temple University student body through flyers posted around campus, in-class announcements in psychology courses, and the Temple University Psychology Research Participation System (a HIPAA compliant online research management system). Students interested in the study were invited to complete an online screening, which included demographic questions, self-report measure of current and lifetime depressive episodes (Inventory to Diagnose Depression- Lifetime; IDD-L; Zimmerman & Coryell, 1987), and measures of depressive symptoms (Beck Depression Inventory-II; BDI-II; Beck, Brown, & Steer 1996) and symptoms of (hypo)mania (7 Up 7 Down Inventory; 7U7D; Youngstrom, Murray, Johnson, & Findling, 2013) to evaluate inclusion and exclusion criteria.

Eligible participants included individuals fluent in written and spoken English between the ages of 18-22 years old, which is a time during which individuals experience a wide variety of stressors (Compas, Wagner, Slavin, & Vannatta, 1986). In addition, eligible participants had to have a history of at least one major or minor (subthreshold) depressive episode, given that individuals with a history of depression are most vulnerable to future depressive episodes (Burcusa & Iacono, 2007). Subthreshold depression was categorized as: 1) having two or more symptoms (one of which must be

depressed mood or anhedonia) nearly all day every day for 2 weeks or more, or 2) having five or more symptoms (one of which is depressed mood or anhedonia) most of the day nearly every day for at least a week, and 3) functional impairment must be present. Including individuals with a full range of past depressive symptoms (both clinical and subclinical past depression) would allow us to examine depression on a continuum and examine these processes in individuals vulnerable to, but not currently experiencing, depression.

Participants were excluded only if they met diagnostic criteria for current Major Depressive Disorder (MDD) based on the IDD-L or current levels of moderate or severe depressive symptoms on the BDI-II (indicated by a score of 20 or higher; Beck et al., 1996). Given the importance of identifying *markers* of stress generation that are distinct from the depression itself, individuals not currently experiencing MDD or with moderate to severe depressive symptoms were excluded. Further, given our interest in depression, participants were excluded who scored greater than 3 for (hypo)mania symptoms on the 7 Up scale of the 7U7D Inventory, which may indicate greater risk for bipolar spectrum disorders. Of the 892 individuals who participated in the screener, 457 (51%) did not endorse a past major or subthreshold depressive episode, 111 (12.44%) met inclusion criteria, but endorsed moderate to severe depressive symptoms currently, and 44 (4.93%) met inclusion criteria, but endorsed current hypomanic symptoms. In addition, 159 (17.83%) were eligible and invited to participate in the study, but did not respond to invitations to complete the study. There were no significant differences on symptoms of depression (t = 1.33, p = .16; d = .16) or hypomania (t = 1.88, p = .06; d = .23), sex (χ^2 = .06, p = .80; OR = 1.07), age (t = .27, p = .79; d = 1.09), or type of depressive

episode (χ^2 = .01, p = .92; OR = .96) between those who completed the study and those who were eligible and did not participate. An additional 19 students participated in the study, but did not meet criteria for a past subthreshold or major depressive episode based on the diagnostic interview, and therefore, were not included in the present analyses. However, there were no differences between those who did and did not meet diagnostic criteria for depression on demographic or clinical variables (all *ts* and χ^2s < 1.11, all *ps* >.29).

Procedure

Eligible individuals were invited to participate in the full micro-longitudinal study, which included a three-hour baseline assessment and two weeks of daily diary surveys. During the baseline assessment, individuals first provided written consent to participate in the full study. Participants then completed questionnaires, a diagnostic interview assessing current and past mood disorders, and the Trier Social Stress Test (TSST), during which participants were connected to physiological equipment to measure heart rate variability. Participants then were asked to remotely complete 14 days of daily diaries to assess the occurrence of daily stressors and depressive symptoms using any device connected with internet capability. Participants were compensated for their participation in the study. This study was approved by the Temple University Institutional Review Board (IRB).

Participants

Participants (N = 105) in the final sample were 19.84 years old on average (SD = 1.17 years) and 76% female. In addition, 71% self-identified as Caucasian, 7% as African American, 6% as Biracial, 14.3% as Asian and 2% as 'Other.' In our sample, 7% also

identified as Hispanic. In terms of sexuality, 80% of participants identified as heterosexual, 12% as lesbian, gay, or bisexual, and 8% as 'Something else' or 'Other.' Although 80% of the sample currently lives in an urban area (e.g., Philadelphia), only 25.7% reported living in an urban area growing up and the majority of participants reported that they previously lived in suburban (59%) or rural (15.2%) areas.

At the diagnostic assessment, 78 (74.3% of the sample) met criteria for past Major Depressive Disorder (MDD) and 27 (25.7%) for a past subthreshold depression. The mean age of first onset of MDD was 15.75 years (SD = 3.28 years) and 15.19 years (SD = 3.23 years) for a subthreshold episode. Of those with MDD, 47 (49.5%) had one MDD episode, 25 (23.8%) had two episodes, and 4.8% had 3 or 4 MDD episodes. Of those only with subthreshold episodes, 23 participants (85.2%) only had one episode. The average length of the most severe depressive episode ranged considerably, with 17% reporting that the depressive episode lasted for greater than a year, 18% for 6 to 12 months, 24% for 2 to 6 months, 16% for 1 to 2 months, 16% for 2 to 4 weeks, and 14% reporting a subthreshold depressive episode that lasted for 1-2 weeks.

Screener Measures

Inventory to Diagnose Depression-Lifetime version (IDD-L; Zimmerman & Coryell, 1987). The IDD-L is a 22-item self-report measure that indexes the number of depressive symptoms that a person has experienced during their worst lifetime period of depression. Each item is rated on a 5-point scale (0 to 4; e.g., 0- "I did not lose interest in my usual activities" to 4 "I have lost interest in all of my usual activities.") to assess the severity, duration, and impairment of clinically significant symptoms of depression. The IDD-L is scored using the criteria for the Diagnostic and Statistical Manual of Mental

Disorders-Fourth Edition (*DSM-IV*) for MDD and Dysthymia. As previously mentioned, individuals who endorsed subthreshold depression (e.g., two or more symptoms (one of which must be depressed mood or anhedonia) nearly all day every day for 2 weeks or more, or five or more symptoms (one of which is depressed mood or anhedonia) most of the day nearly every day for at least a week) were included. Functional impairment also must be present to meet for a diagnosis of any depressive disorder. This scale has excellent sensitivity and specificity for diagnoses made using structured diagnostic interviews (Zimmerman & Coryell, 1987). In the present study, the internal reliability was $\alpha = .94$.

Beck Depression Inventory-II (BDI; Beck et al., 1996). The BDI-II is a 21-item self-report questionnaire that assesses cognitive, affective, and somatic depressive symptoms experienced over the past 2 weeks. Items are scored on a Likert-scale (0-3), with higher scores indicative of more severe depression. The BDI-II has demonstrated strong psychometric support, including good internal consistency, test-retest reliability ($r = .93$), concurrent validity, and convergent validity (Beck et al., 1996; Beck, Steer, Ball, & Rainieri, 1996). In the current study, the BDI-II had good internal consistency ($\alpha = .90$).

7 Up 7 Down Inventory (7U7D; Youngstrom et al., 2013). The 7U7D is a 14-item measure of manic and depressive tendencies of an individual. Participants respond using a 4-point scale based on frequency of experience (1- *Never or hardly ever* to 4- *Very often or almost constantly*). Only the 7 Up subscale of the 7U7D was used in the present study to determine the presence of manic or hypomanic symptoms. Item scores of 3 or 4 were recoded as 1, and item scores of 1 or 2 were recoded as 0 (Youngstrom et al.,

2013). All items then were summed for a total score, with scores ranging from 0-7. In the present study, individuals with scores greater than 3 were deemed ineligible, given findings that 3 or more on the 7U is associated with clinically significant (hypo)mania (Alloy, 2016, personal communication).

Baseline Assessment

Diagnostic Interview. An expanded version of the Schedule for Affective Disorders and Schizophrenia - Lifetime (exp-SADS-L; Alloy et al., 2008; Endicott & Spitzer, 1978) is a semi-structured diagnostic interview used to assess past and current psychopathology. The present study only utilized the depression and bipolar modules of the exp-SADS-L to determine whether individuals' depressive symptomatology met criteria for past major or minor/subthreshold depressive disorder according to Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (*DSM-5*) criteria (for inclusion criteria), and current MDD or bipolar disorder (for exclusion criteria). In the present study, subthreshold depression was defined as having five or more symptoms of depression nearly all day every day for one week (N = 15; 14% of full sample) or two or more symptoms all day nearly every day for 2 weeks (N = 12; 11%). Consistent with *DSM-5* criteria, depressed mood or anhedonia and significant associated functional impairment must be present to meet criteria for any depressive disorder. In prior studies, the exp-SADS-L has demonstrated excellent inter-rater reliability, with $\kappa > .90$ for unipolar depression diagnoses based on 80 jointly rated interviews (Alloy et al., 2000) and $\kappa > .96$ for bipolar disorder diagnoses based on 105 jointly rated interviews (Alloy et al., 2008). In the present study, all interviews were audio-recorded for reliability coding and we examined agreement on presence of symptoms and diagnosis on a randomly

selected 20 interviews. Reliability raters were blind to the outcome of the original interview. Our interviewers demonstrated excellent agreement ($\kappa = .95$, $p < .001$).

Trier Social Stress Test (TSST). The TSST is a valid, reliable, and widely used method to induce psychosocial stress and elicit an autonomic stress response (Kudielka, Buske-Kirschbaum, Hellhammer, & Kirschbaum, 2004; Phillips, Ginty, & Hughes, 2013). The TSST consists of socio-evaluative threat of a public speaking task and performance threat of mental arithmetic. First, participants were instructed to sit still and breathe normally for three minutes to establish baseline levels of HRV. To increase the socio-evaluative threat for late adolescents, after the baseline assessment of HRV, participants were informed that they would be asked to give a 3-minute speech about themselves in front a camera (where they would be seeing themselves on screen) and the video would be recorded and streamed live to a group of their peers who would rate how much they liked them and would want to spend time with them. In addition to participants viewing themselves on the screen, the experimenter also was present and silently observed the speech and math calculations, while pretending to take notes on the participants' speech and behavior. Prior to beginning the speech, participants were instructed to think about and prepare their speech (without writing anything down) for the next three minutes while the interviewer left the room. After three minutes elapsed, participants were instructed to give a speech for the full three-minutes while seeing themselves on the screen. After three minutes, participants were instructed to complete a calculation task (subtracting increments of 13 from 2,083) until asked to stop, which was after 60-seconds elapsed. The participants then were told to breathe normally for the next three minutes until the task was over to monitor physiological recovery.

Heart Rate Variability (HRV). Electrocardiogram (ECG) data were measured using a BioPac BioHarness MP150 with AcqKnowledge v. 4.2 software, a system that monitors, analyzes, and records physiological parameters (Biopac Systems, Inc., Santa Barbara, CA). The BioHarness is a wireless device that is attached to individuals via a standard three-electrode setup sampled at 1000 Hz. Heart rate was monitored continuously during the TSST, with markers placed throughout the experiment to indicate the beginning and end of each component of the TSST. There were four distinct epochs in the present study: baseline, anticipatory threat, stressor task, and recovery. Data collected from Acknowledge then were visually inspected for artifacts and corrected manually using Kubios HRV software (version 2.2; http://kubios.uku.fi/). Power spectral analysis was conducted by integrating the power estimates over each frequency band with a fast Fourier transformation for each phase of the TSST. Consistent with the recommendations by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996), the absolute power density (ms^2) for each band of high-frequency (HF; .15 - .50 Hz) and low frequency (LF; .04 -.15), and Very Low Frequency (VLF; 0 - .04) was calculated and the average for each period was used. Only HF HRV was included in subsequent analyses because of our focus on HF-HRV (hereafter referred to as RSA). RSA variables were log-transformed to normalize the distribution, which violated normality assumptions, prior to calculating variables (Bylsma et al., 2014; Yaroslavsky et al., 2013). In the present study, RSA reactivity was calculated by subtracting the RSA during the full stressor (speech and math) from RSA during the baseline period. Although RSA for anticipatory threat and recovery also were recorded and analyzed in the Kubios HRV program, we did not

include the anticipatory threat or recovery following stress in the present study given our focus on resting RSA and reactivity to stress[1].

PROMIS-depression-Long Form (PROMIS-depression-LF; Pilkonis et al., 2011). The Patient Reported Outcomes Measurement Information System (PROMIS) network used Item Response Theory to develop a measure to assess depression as per the National Institutes of Health initiatives. The PROMIS-Depression-LF is a 27-item measure that assesses the severity of symptoms of depression. It measures the presence of depressive symptoms over the prior two weeks. The PROMIS-Depression-LF has been found to have better psychometric properties and be more sensitive to the dimensionality of depressive severity than other well known self-report scales of depression (Olino et al., 2012; Olino et al., 2013; Pilkonis et al., 2011). The PROMIS-Depression-LF was used as a covariate for analyses predicting to depressive symptoms over the subsequent two weeks using the short form of this measure (see below). In the present study, the internal reliability of the PROMIS-Depression-LF was $\alpha = .97$.

Life Events Scale (LES) and Interview (LEI; Safford et al., 2007). The LES asks individuals to indicate which events occurred to them over the past four weeks (specific dates and a calendar are provided to the participant). The LES includes 100 major and minor life events in a variety of domains, including school, work, finances, family, peer, and romantic relationships. Then, individuals were interviewed to validate that the events occurred during the given period and met a priori definitional criteria to reduce potential biases. The LES events were a priori rated on the extent to which they

[1] Although some research has averaged the epochs of pre-and post-task rest periods, reduced recovery from socioevaluative stressors has been demonstrated among adults with MDD (Bylsma et al., 2014). Thus, poorer RSA recovery may bias a calculation of baseline using both RSA epochs.

were independent (fateful) or dependent (i.e., an event to which an individual would be expected to contribute), and individually adjusted accordingly based on information provided by the participant (Safford et al., 2007). Dependent events also were categorized as interpersonally-related in the present study. In this study, the LES and LEI were administered at baseline to control for the effects of prior stressors on physiological variables. Thus, only interpersonal dependent and independent stressors were included in the present study. The LES and LEI have demonstrated excellent reliability and validity (Safford et al., 2007).

Daily Diary

For the convenience of participants and feasibility, participants were emailed the daily survey each day at 6PM and instructed to complete the daily diary between the hours of 6PM-12AM. This time frame was designed to allow participants ample time to complete the diary due to school and work obligations. Participants were instructed to report any events that occurred since they last completed the diary the previous day. In the event that participants did not complete the survey the day before, they were instructed to complete the survey based on the past 24 hours. Participants also were emailed daily reminders to complete the diary if the diary was not completed by 10PM each night.

Daily Diary Events. To assess stressors that participants experienced each day, participants completed the Daily Diary, which included 26 events that are both major and minor negative events in the daily lives of late adolescents with a focus on achievement (e.g., did poorly on a graded assignment) and social events (e.g., excluded or left out by group of friends). Interpersonal events also included a checklist for participants to

endorse multiple parties involved (e.g., family, friend, significant other, coworker, or other). For instance, for the event "I got into a fight or argument with someone," participants were able to select any individual to which the statement applied. This enabled us to more comprehensively assess events that could have occurred within one item. Thus, there were a total of 64 possible items that participants could have endorsed across the entire daily diary. At the end of the daily diary, participants were invited to report additional events that may have occurred but are not represented in the diary. Examples reported included: "My family and I had to attend a funeral today," "I woke up with hives today," "My dog had a seizure today," "My apartment flooded," "I missed my train and was late for class." All endorsed and added events were coded based on whether or not the event occurred that day (0 = no; 1 = yes). All of these events were *a priori* categorized as *dependent* (i.e., a result of the individual's behaviors or characteristics; Liu & Alloy, 2010) or *independent* (i.e., fateful events), and adjusted based on contextual information (Francis-Raniere, Alloy, & Abramson, 2006). In total, there were 38 dependent events and 26 independent events (e.g., "I had a minor illness or injury"), in addition to events added by the participant. Of these, 23 events were interpersonal dependent events (e.g., "I had a fight or conflict with a friend"). As noted above, interpersonal stress generation is evidenced by the occurrence of events that are dependent within interpersonal relationships (Liu & Alloy, 2010). Thus, the present study focused on events that were *interpersonal dependent,* but independent events also were examined to determine specificity of relationships between RSA patterns and *dependent* events. On average, participants completed an average of 12.20 (87.14%; range 6-14; *SD* = 2.03) diaries out of the 14 diaries over the two-week period.

PROMIS-depression-Short Form (PROMIS-depression- SF; Pilkonis et al., 2011). The PROMIS-Depression-SF is an 8-item measure that assesses the severity of symptoms of depression. Although the measure typically inquires about depressive symptoms over the past two weeks, the present study adapted it to assess depressive symptoms on a daily basis and was included on the daily diary measures. The PROMIS-Depression-SF also has been found to have sound psychometrics similar to the longer version (Olino et al., 2012; Olino et al., 2013; Pilkonis et al., 2011). In the present study, the internal reliability of the PROMIS-Depression-SF was $\alpha = .90$.

Statistical Analyses

Preliminary Analyses. Preliminary analyses were conducted using SPSS Version 21.0 (IBM Corp., 2012). Specifically, *t*-tests examining differences in the primary variables of interest (RSA, average daily interpersonal dependent stressors, independent stressors, depressive symptoms) as a function of sex and depression history (MDD versus subclinical) were conducted. We also conducted paired-samples *t*-tests comparing HRV levels at each phase of the stressor task to ensure that the stressor task induced the expected physiological stress. Bivariate correlations between the primary variables of interest also were examined.

Primary Hypothesis Testing Analyses. To determine whether physiological reactivity predicted daily stress generation and depressive symptoms, multilevel modeling (MLM) using Mplus 7.0 (Muthen & Muthen, 2007) was used to test hypotheses. This provided for more accurate and powerful tests than is possible with a nomothetic (sample mean-centered) approach. For our analyses, there were two levels of data, including the daily diary assessments (Level 1) nested within the individual (Level

2). Thus, data (e.g., stressors and depressive symptoms) from the 14 daily assessments are Level 1 variables and data from the Time 1 assessment (e.g., resting RSA and RSA reactivity) are Level 2 variables. MLM also is advantageous because it uses Maximum Likelihood to estimate parameters for individuals with missing data (e.g. missing one daily diary assessment), which maximizes data use and prevents unnecessary exclusion of participants from analyses.

Direct Effects. We examined whether resting RSA or reactivity to the lab-induced stressor predicted depressive symptoms and interpersonal stress generation over the two weeks of daily diary assessments. Thus, resting RSA and RSA reactivity were entered as Level 2 variables for all analyses. For our first hypothesis, daily depressive symptoms were entered as the Level 1 outcome variable. For our second hypothesis, the total number of interpersonal dependent stressors from the daily diary assessments was entered as the Level 1 outcome variable. Thus, participants' resting RSA and RSA reactivity predicted the intercept of depressive symptoms and interpersonal dependent stressors across the daily diary study assessments. For our results to indicate stress generation, it is crucial that resting RSA and RSA reactivity *only* predict to interpersonal dependent stressors and not independent stressors. Thus, independent stressors also were examined to confirm the specificity of findings to the generation of dependent events. All analyses were conducted covarying for history of major depressive disorder and sex, as well as depression medication use, heart condition, and body mass index. We also covaried for Time 1 depressive symptoms, Time 1 interpersonal dependent, and Time 1 independent events (respectively, when each was examined as the outcome) that occurred in the

previous four weeks to ensure that atypical RSA patterns prospectively predicted depressive symptoms and stressors controlling for previous effects.[2]

In addition, to examine the potential interactive effects of resting RSA and RSA reactivity predicting interpersonal stress generation and depressive symptoms given research on the potential interactive effects of resting RSA and RSA reactivity in depression (Yaroslavsky, Rottenberg, et al., 2013), we centered resting RSA and RSA reactivity and created an interaction term between them predicting interpersonal dependent stressors and depressive symptoms. When there was evidence of a significant interaction, we probed the interaction at high and low levels (plus or minus 1 SD) of the moderator.

Mediational Hypotheses. To test our mediational hypotheses that stress generation would mediate the relationship between physiological reactivity and depressive symptoms, we conducted three mediational analyses within a 2-1-1 multilevel modeling framework with resting RSA, RSA reactivity, and the interaction of resting RSA and RSA reactivity separately. Thus, resting RSA, RSA reactivity, and resting RSA x RSA reactivity were entered as the Level 2 predictor variables for each of these analyses. The number of daily interpersonal dependent stressors from the daily diary assessments was entered as the Level 1 mediating variable and daily depressive symptoms was entered as the Level 1 dependent variable, controlling for previous levels of depressive symptoms (lagged depressive symptoms). For all mediation analyses, we regressed the dependent and mediating variables on the predictor variable (RSA) and all covariates (lifetime

[2] Analyses were conducted with all HRV indices separately and simultaneously (as well as with and without covariates). However, the pattern of results was similar across all analyses, so only the analyses with all HRV indices and covariates are presented.

depression medication use, BMI, sex, heart condition, Time 1 depression, and prior life events). We also regressed the dependent variable on the mediating variable and covariates. Thus, we examined each part of the mediation model with resting RSA, RSA reactivity, and the interactive effects predicting dependent stressors and depressive symptoms and dependent stressors predicting depressive symptoms separately. We also estimated the slope of the within- person effects for interpersonal dependent stressors on depressive symptoms and constrained the slope of the between-person effects of interpersonal dependent stressors on depressive symptoms to be equal. There are other methods to testing mediation in multilevel modeling (such as not constraining these effects in the between-level), but we conducted our analyses with the traditional 2-1-1 approach to multilevel mediation.

Further, we tested the indirect effect of resting RSA, RSA reactivity, and their interaction on daily depressive symptoms via stress generation. The indirect effect is calculated by estimating the interactive effects (a*b) of the independent to mediating variable (a) and mediating variable to dependent variable (b). Although direct effects are deemed to be important for mediation in traditional mediation models (Baron & Kenny, 1986), more recent statistical approaches indicate that indirect effects may be present even without a significant direct effect between the independent and dependent variables (Hayes, 2009). Thus, we conducted our mediational analyses as planned regardless of whether there was a significant direct effect. Although bootstrapping is the recommended approach for tests of mediation, bootstrapping in multilevel models is a continued area of research and Mplus 7.0 does not allow for bootstrapping in these analyses.

Exploratory Statistical Analyses. Further, to investigate whether there were potential sex differences in these relationships, we conducted additional analyses using an interaction term between resting RSA and sex or RSA reactivity and sex predicting daily depressive symptoms and interpersonal stress generation (conducted separately). When there was evidence of a significant interaction, we probed the interaction for males and females separately to understand the direction of the effect. Thus, the full interaction term and the simple slopes for males and females are presented.

Results

Preliminary Analyses

Bivariate correlations for the primary variables of interest are shown in Table 1. As expected, higher resting RSA levels were significantly associated with greater RSA reactivity. However, RSA variables were not associated with stressors or depressive symptoms across the daily assessments. Interestingly, interpersonal dependent and independent stressors also were not correlated, and only interpersonal dependent stressors were significantly correlated with depressive symptoms. We also compared individuals by sex on mean levels of primary study variables and found no significant differences (see Appendix A, Table 10).

Table 1. Bivariate Correlations Among Primary Study Variables

	Measure	1	2	3	4	5
1	Resting RSA	-				
2	RSA Rx	.56***	-			
3	Int Dep Stress	.05	-.18	-		
4	Indep Stress	-.05	.13	.17	-	
5	Dep Sx	-.15	-.08	.21*	.15	-

Note. * p <. 05; ** p < .01; *** p < .001. RSA = Respiratory Sinus Arrhythmia; Rx = Reactivity; Int Dep = Interpersonal Dependent; Indep = Independent; Dep Sx = Depressive Symptoms.

Next, we evaluated whether there were significant differences across each phase of the stressor task (Baseline, Anticipation, Stressor, Recovery) for the full sample (Table 2). These analyses revealed that, as expected, participants experienced increases in heart rate across each phase of the stressor task, from baseline to anticipation (t = 10.782, p <. 001; d = .58), anticipation to stressor (t = 13.34, p <. 001; d = .78), and baseline to stressor (t = 18.17, p < .001; d = 1.33), as well as decreases from stressor to recovery (t = -17.27, p <. 001; d = 1.31). In addition, participants on average experienced the expected decreases in RSA from baseline to stressor (t = -5.73, p <. 001; d = .54) and increases in RSA from stressor to recovery (t = 3.98, p < .001; d = .38). However, there were no differences in RSA from baseline to anticipation (t = -1.19, p = .24; d = .07). These findings suggest that our stressor task induced physiological stress for most participants.

Clinical versus Subclinical Depression. Demographic characteristics and primary study variables are displayed in Table 2 for the overall sample and by diagnostic category. Although the main hypothesis testing analyses were conducted with participants with both clinical and subclinical depression, we examined the study variables by depression history to better understand the characteristics of our sample. There were no significant differences between those with clinical and subclinical depression history on demographic (age, race, sex) and clinical variables (e.g., age of first onset, depression symptoms), with the exception of lifetime depression medication use (t = 3.75, p < .05). Specifically, individuals with a history of MDD were more likely to report having used depression medication in the past than those with only a subclinical episode, which has been found to result in blunted RSA (Licht et al., 2008) and thus,

Table 2. Descriptive Statistics and Physiological Characteristics Across Sample by Depression History

Measure	Overall Sample (N = 105)		MDD (N = 78)		Subthreshold (N = 27)		Statistical Difference
	M (N)	*SD (%)*	*M (N)*	*SD (%)*	*M (N)*	*SD (%)*	*t* (X^2)
Demographic							
Sex (Female)	80	76.92	62	79.49	18	66.67	1.82
Race (White)	75	72.12	56	71.79	19	70.37	.02
Age	19.84	1.17	19.90	1.15	19.67	1.24	.88
BMI	23.71	3.80	23.90	4.03	23.17	3.07	.86
RSA							
Baseline RSA	6.50	1.12	6.56	1.09	6.31	1.21	.97
Anticipatory RSA	6.42	1.14	6.41	1.18	6.45	1.04	.18
Stressor RSA	5.92	1.02	5.91	1.03	5.94	1.01	.14
Recovery RSA	6.33	1.13	6.36	1.16	6.22	1.02	.55
HR							
Baseline HR	75.44	10.06	75.17	9.96	76.23	10.47	.47
Anticipatory HR	81.65	11.27	81.78	12.02	81.29	8.96	.19
Stressor HR	91.61	14.00	91.55	14.54	91.75	12.59	.06
Recovery HR	75.48	10.33	75.17	10.35	76.46	10.42	.54
Daily Diary							
PROMIS-Dep	10.95	3.10	11.37	3.38	9.73	1.59	3.35***
Int Dep Stress	1.51	.52	1.55	.57	1.36	.30	.2.17*
Indep Stress	.36	.34	.38	.36	.31	.27	.97

Note. * $p <$. 05; ** $p <$ .01; *** $p <$ .001. MDD = Major Depressive Disorder (Coded as 0 = None; 1 = Present); BMI = Body Mass Index; RSA = Respiratory Sinus Arrhythmia; HR = Heart Rate; Int Dep = Interpersonal Dependent; Indep = Independent; Dep Sx = Depressive Symptoms.

were controlled for all analyses. In terms of physiological differences, there were no significant differences in RSA or HR between those with past MDD and subclinical depression during baseline, anticipation, stressor, recovery, or RSA reactivity from baseline to stressor (t = 1.22, p = .23). In addition, individuals with a history of MDD reported greater depressive symptoms on average during the daily diaries than those with subclinical depression history, as well as greater interpersonal dependent stressors (but not independent stressors). We also evaluated the effects of resting RSA and RSA reactivity on depressive symptoms and interpersonal stress generation as a function of MDD history, and found no significant interactions. Therefore, we did not include this in the present study, but results are available upon request.

Primary Hypothesis Testing Analyses

Daily Depressive Symptoms. In partial support of our hypotheses, only resting RSA predicted depressive symptoms over the two weeks of daily diary assessments (Table 3). This relationship was such that lower resting RSA levels predicted more subsequent depressive symptoms over the two-week period (intercept), controlling for MDD history, sex, BMI, depression medication, heart condition, and Time 1 depressive symptoms. However, there was no effect of RSA reactivity on depressive symptoms over the daily diary assessments (Table 3). In addition, contrary to prior literature, there was no significant interaction between resting RSA and RSA reactivity predicting depressive symptoms (see Appendix A, Table 11).

Table 3. Main Effects of Resting RSA and RSA Reactivity on Depressive Symptoms

Variable	Depressive Symptoms		
	B	*SE*	*t*
Between-level			
Intercept (Dep Sx)	9.75	2.32	4.21***
MDD	.1.12	.56	1.98*
Sex	.58	.60	.98
Past Dep Med	.82	.61	1.35
BMI	.04	.06	.66
Cardio	2.25	.29	.77
T1 Dep Sx	.07	.01	6.24***
Resting RSA	-.55	.26	-2.11*
RSA Rx	.22	.29	.77
Random Effects			
Intercept (Dep Sx)	4.82	.82	5.91***

Note. * $p <$ .05; ** $p <$ .01; *** $p <$ .001. Dep Sx = Depressive Symptoms; MDD = Major Depressive Disorder (Coded as 0 = None; 1 = Present); Dep Med = Depressive Medication Use; BMI = Body Mass Index; Cardio = Heart condition; T1 = Time 1; RSA = Respiratory Sinus Arrhythmia; Rx = Reactivity.

Daily Stress Generation. Consistent with our hypotheses, there was a main effect of RSA reactivity on daily interpersonal dependent stressors (Table 4), controlling for MDD history, sex, BMI, depression medication, heart condition, and Time 1 interpersonal dependent stressors that occurred in the previous four weeks. However, there was no direct effect of resting RSA predicting interpersonal dependent stressors. Further, consistent with our hypotheses and stress generation literature, there were no direct effects of resting RSA or RSA reactivity predicting independent stressors. In addition, our analyses examining the combined effects of resting RSA and RSA reactivity indicated that there was no significant interactive effect on daily interpersonal dependent stressors or independent stressors (see Appendix A, Table 12).

Table 4. Main Effects of Resting RSA and RSA Reactivity on Stressors

Variable	Interpersonal Dependent Stressors		
	B	*SE*	*t*
Between-level			
Intercept (Int dep Stress)	.62	.45	1.40
MDD	.13	.11	1.14
Sex	.11	.12	.83
Past Dep Med	.17	.12	1.43
BMI	.02	.01	1.23
Cardio	.38	.29	1.29
T1 Neg Int Dep	.05	.02	2.22*
Resting RSA	.08	.05	1.62
RSA Rx	-.13	.06	-2.32*
Random Effects			
Intercept (Int dep Stress)	.18	.03	5.70***

Variable	Independent Stressors		
	B	*SE*	*t*
Fixed Effects			
Intercept (Indep Stress)	.44	.28	1.69
MDD	.04	.07	.56
Sex	.08	.08	1.04
Cardio	-.04	.18	-.21
Dep Med	-.05	.07	-.77
BMI	.03	.01	3.66***
T1 Indep Stress	.06	.02	3.45***
Resting RSA	-.01	.03	-.27
RSA Rx	-.05	.0	-1.54
Random Effects			
Intercept (Indep Stress)	.06	.01	4.81***

Note. * p <. 05; ** p < .01; *** p < .001. Int dep = Interpersonal dependent; MDD = Major Depressive Disorder (Coded as 0 = None; 1 = Present); Dep Med = Depressive Medication Use; BMI = Body Mass Index; Cardio = Heart condition; T1 = Time 1; Neg = Negative; RSA = Respiratory Sinus Arrhythmia; Rx = Reactivity; Indep = Independent

Stress Generation as Mediator of RSA Reactivity and Depressive Symptoms. When examining the relationship between our mediating and dependent variables, there was a direct relationship from daily interpersonal dependent stressors to depressive symptoms (B = .83; SE = .14; $t = 6.16$, $p < .001$), even controlling for prior day depressive symptoms. For our first round of mediation analyses, although there was no evidence of a significant direct effect from RSA reactivity to depressive symptoms, there was a significant indirect effect of RSA reactivity on depressive symptoms via interpersonal stress generation (B = -.11, SE = .05, $t = -2.03$, $p = .04$; CI [95%]= -.21 - -.003). Specifically, these findings indicated that blunted levels of RSA reactivity (or less RSA withdrawal) predicted greater interpersonal dependent stressors, which, in turn, predicted to greater depressive symptoms. To confirm that this effect was specific to interpersonal dependent stressors, we evaluated the effect of RSA reactivity to depressive symptoms via independent stressors and found there was no significant indirect effect (B = -.33, SE = .04, $t = -.88$, $p = .38$). In addition, although there was a direct effect from lower resting RSA to depressive symptoms, our results indicated that this was not mediated by interpersonal stress generation (i.e., no significant indirect effect; B = .06, SE = .05, $t = 1.30$, $p = .19$). Further, there was no indirect effect from the combined indices of resting RSA and RSA reactivity to depressive symptoms via interpersonal dependent stressors (B < .01, SE = .03, $t = .09$, $p = .93$).

Exploratory Statistical Analyses.

Sex Differences. Our first exploratory analysis examining whether resting RSA predicted depressive symptoms differently among males and females indicated that there was a significant interaction between resting RSA and sex predicting depressive

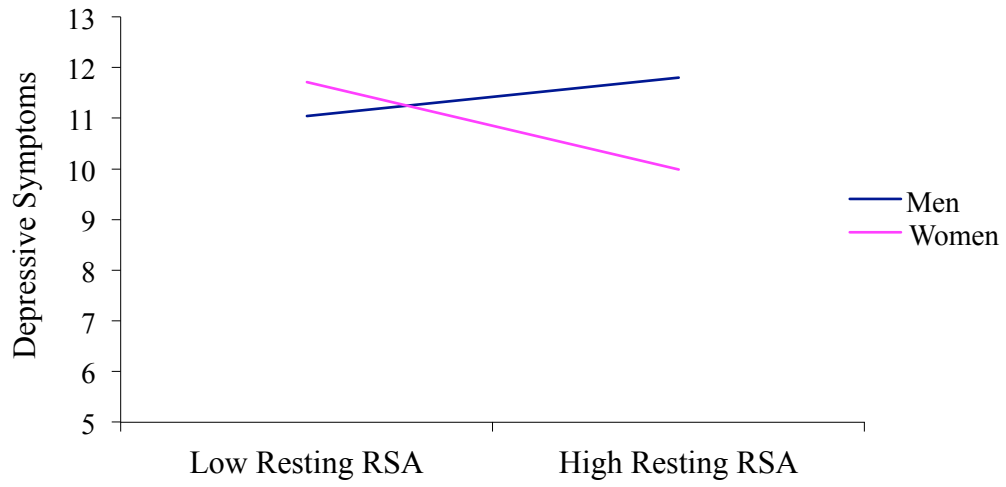
symptoms (Table 5; Figure 1). The nature of this interaction was such that the association between resting RSA and subsequent depressive symptoms was significant only for late adolescent girls (B = -.86, SE = .29; t = -3.03, p < .01), but not for late adolescent boys (B = .38, SE = .46; t = .82, p = .41). Specifically, girls with lower resting RSA were more likely to report depressive symptoms compared to girls with greater resting RSA, who had the lowest depressive symptoms. However, there was no relationship between resting RSA and depressive symptoms for boys. Also, there was no interaction between RSA reactivity and sex in predicting to depressive symptoms (B = -.18, SE = t = .72, p = .80; see Appendix A, Table 13). Finally, there were no sex differences predicting interpersonal dependent stressors for resting RSA (B = -.08, SE = .10; t = -.79, p = .43) or RSA reactivity (B = -.19, SE = .14; t = -1.35, p = .18; see Appendix A, Table 14).

Table 5. Interactions of Resting RSA and Sex Predicting Depressive Symptoms

Variable	Depressive Symptoms		
	B	*SE*	*t*
Fixed Effects			
Intercept (Dep Sx)	11.16	2.33	4.79***
MDD	1.08	.55	1.96*
Sex (Female 0)	-7.55	3.45	-2.19*
Past Dep Med	.90	.59	1.53
BMI	.04	.06	.70
Cardio	1.98	1.41	1.41
T1 Dep Sx	.07	.01	6.30***
RSA Rx	.33	.28	1.18
Resting RSA	-.86	.29	-3.03***
Resting RSA x Sex	1.25	.52	2.39*
Random Effects			
Intercept (Dep Sx)	4.52	.77	5.84***

Note. * p <. 05; ** p < .01; *** p < .001. Dep Sx = Depressive Symptoms; MDD = Major Depressive Disorder (Coded as 0 = None; 1 = Present); Dep Med = Depressive Medication Use; BMI = Body Mass Index; Cardio = Heart condition; T1 = Time 1; RSA = Respiratory Sinus Arrhythmia; Rx = Reactivity.

Figure 1. Sex Differences in the Effects of Resting RSA on Depressive Symptoms



Discussion

Considerable research has documented the atypical and dysregulated patterns of resting RSA and RSA reactivity exhibited among individuals with depression, including current and remitted depression, and elevated depressive symptoms (Bylsma et al., 2014; Yaroslavsky et al., 2014; Rottenberg, 2007). However, less research has moved beyond this to examine the role of RSA, particularly RSA reactivity, in processes known to confer risk for depression. In particular, stress generation is a robust predictor of depression onset and recurrence, and vulnerabilities to depression have been found to predict the occurrence of stressors (Liu, 2013; Liu & Alloy, 2010). Given the importance of RSA and stressful life events as predictors of depression, it is surprising that no known study has examined resting and fluctuating RSA levels in the process of stress generation. Thus, the first goal of the present study was to examine resting RSA and RSA reactivity (and their interactive effects) as predictors of prospective interpersonal stress generation and depressive symptoms among individuals with a history of depression. Further, the

second goal of our study was to examine whether interpersonal stress generation served as a mediator of the relationship between resting RSA and reactivity and depressive symptoms, thereby increasing the risk for depression recurrence. Finally, given the higher rates of depression among women and sex differences in RSA (Chambers & Allen, 2007; Hankin et al., 1998), our third goal was to explore potential sex differences in these relationships.

First, our preliminary results suggest that our stressor, the Trier Social Stress Test, induced physiological stress among most individuals, as the majority of individuals exhibited the expected heart rate increase and RSA withdrawal to the socio-evaluative stressor. Interestingly, however, our finding that individuals with a history of MDD did not differ from those with a subclinical depression history on resting RSA and RSA reactivity extends prior research on RSA in depression. Specifically, individuals with only a subclinical episode of past depression exhibited similar levels of RSA at rest and RSA fluctuation in response to the stressor as those with a history of MDD. Although we were unable to compare these groups to healthy controls, and consequently, to determine whether these groups have unique RSA patterns from never-depressed individuals, this finding represents an important step in evaluating the heterogeneity of depression in psychophysiological processes. According to the findings of our study, there are not meaningful differences between individuals with past clinical and subclinical depression on RSA patterns, which suggests that these individuals may demonstrate similar levels of adaptive (and maladaptive) physiological self-and stress-regulation following depressive episodes. However, it is important to note that there may still be differences in RSA

patterns between individuals with *current* major and subthreshold depression, which we did not examine in the present study.

One of the main findings of the present study was that lower resting levels of RSA, but not RSA reactivity, prospectively predicted depressive symptoms over two weeks of daily diary assessments, controlling for depressive symptoms at the initial assessment, major depressive episode history, and a number of variables associated with RSA (heart condition, depression medication, BMI). Specifically, formerly depressed individuals with lower resting RSA experienced greater daily depressive symptoms on average than those with higher levels of resting RSA. This finding is consistent with prior research indicating that lower RSA is associated with greater depressive symptoms one year later (Vasquez et al., 2016), but highlights the impact of resting RSA on daily depressive symptoms and extends these findings to a sample of late adolescents with a major or subclinical depression history. To our knowledge, this is the first study to document that individual differences in RSA predict subsequent depressive symptoms among individuals with remitted depression, which is notable given that individuals with a history of depression typically exhibit lower levels of RSA than never-depressed individuals (Yaroslavsky et al., 2014). These results suggest that formerly depressed individuals with lower resting RSA may be at greater risk for a depression recurrence than individuals with a history of depression and higher resting RSA.

Consistent with our hypotheses, our second main finding was that only RSA reactivity significantly predicted more interpersonal dependent stressors over the next two weeks, controlling for previous interpersonal dependent stressors, depression history, and cardiac-related variables. Further, these results were specific to interpersonal

dependent stressors and did not occur for independent stressors, which is consistent with the stress generation theory that individuals' characteristics or behaviors would only be expected to contribute to dependent events (Hammen, 1991). These findings suggest that individuals with *less* RSA reactivity prospectively contributed to subsequent interpersonal *dependent* stressors, but not independent stressors, controlling for RSA-related variables and stressors that occurred in the prior four-week period. Thus, it is possible that individuals who are not able to effectively and adequately mobilize resources to respond to changing or stressful environmental demands may inadvertently generate more negative stressful events, especially in their interpersonal relationships. Specifically, blunted RSA reactivity may result in certain negative interpersonal behaviors, such as lack of interpersonal warmth, social disengagement, and maladaptive affective responses (Diamond & Cribbett, 2013; Porges, 2003a), that reduce interpersonal functioning and elicit more negative daily interactions or stressors with friends, family, romantic partners, or coworkers. Further, our mediational findings suggest that the occurrence of interpersonal dependent stressors, in turn, predicts higher levels of daily depressive symptoms, controlling for prior day depressive symptoms. It is particularly notable that these findings are documented among individuals with a history of depression, who already are at risk for stress generation (Liu & Alloy, 2010). This suggests that blunted RSA reactivity may be a predictor of stress generation and subsequent depressive symptoms among individuals who are formerly depressed, and potentially distinguish those who are at greater risk for depression recurrence.

Notably, we did not find main effects of resting RSA on interpersonal dependent stressors or direct effects of RSA reactivity on depressive symptoms. However, we did

find evidence of an indirect effect for blunted RSA reactivity on depressive symptoms via interpersonal stress generation. Specifically, individuals with *less* RSA reactivity experienced more average daily stress generation, which, in turn, predicted greater daily depressive symptoms. This suggests that only resting RSA may directly predict depression, but RSA reactivity contributes to maladaptive interpersonal processes (i.e., stress generation) that predict greater levels of depressive symptoms. These findings suggest that there may be something specific about RSA reactivity's role in interpersonal stress generation, and resting RSA's role as a predictor of depressive symptoms. For instance, it could be that resting RSA is a better index of depressive symptoms and affect dysregulation, whereas RSA reactivity may be associated more strongly with stress-specific regulation and maladaptive responses to stress, which elicits stress generation. Our lack of support for a mediational effect of resting RSA to depressive symptoms via stress generation supports this, and suggests that there may be other mechanisms through which resting RSA contributes to depression. One possibility could be that individuals with lower resting RSA have greater emotional reactivity and regulation difficulties, as research indicates that individuals with lower resting RSA take longer to recover from emotional arousal and negative mood states (Thayer & Lane, 2000).

Further, we did not find any significant interactions between resting RSA and RSA reactivity on interpersonal stress generation or depressive symptoms, which is in contrast to prior research on atypical RSA patterns and depression (Yaroslavsky, Rottenberg et al., 2013; Yaroslavsky, Bylsma, et al., 2013; Yaroslavsky et al., 2014). One possible explanation for these discrepant findings may be that the present study utilized a socio-evaluative stressor for our stressor task, whereas these prior studies (Yaroslavsky et

al., 2014) used an emotion-induction task, which may elicit different patterns of RSA response (Panaite et al., 2016). It is also possible that the short-term nature of our study design precluded our ability to detect effects of RSA patterns over longer intervals.

In contrast to several studies of current depression (Chambers & Allen, 2007; Thayer et al., 1998), we did not find any sex differences in resting RSA or RSA reactivity among individuals with past depression. Although there weren't sex differences in resting RSA, we did find that the predictive association between lower levels of RSA and daily depressive symptoms was qualified by significant sex differences. Specifically, our exploratory analyses examining potential sex differences in the link between RSA and depression indicated that the effects of resting RSA was particularly pronounced among women. This relationship was such that women with lower resting RSA were significantly more likely to have daily depressive symptoms than women with higher levels of resting RSA, whereas resting RSA did not predict depressive symptoms for men. However, there were no significant sex differences in the effects of resting RSA or RSA reactivity on interpersonal stress generation, or RSA reactivity on depressive symptoms. Thus, it appears that there is something specific about higher resting RSA that is protective for women with a history of depression, whereas lower resting RSA contributed to elevated depressive symptoms in women. Thus, women with lower resting RSA may be particularly vulnerable to depressive symptoms, thereby heightening the risk for future depression. It is interesting that there was no effect of resting RSA on depression for men, who exhibited high levels of depressive symptoms regardless of their RSA levels. One possibility is that this is due to the smaller number of men in the study, which may have limited the variance of our variables (RSA, depressive symptoms,

stressors). Thus, future research should examine potential sex differences in the relationship between resting RSA and depressive symptoms with a more evenly distributed sample by sex.

Although our study has a number of strengths, including a micro-longitudinal design and sample with past clinical depression, there are also several weaknesses that should be addressed to enhance future research. First, we only included a sample of individuals who experienced past major or subclinical depression, but did not have groups of healthy controls or individuals currently depressed. Including three groups with this design would provide more information about the unique and common elements of resting RSA and RSA reactivity that confer risk for depression and depression-related processes. In addition, although we examined sex differences, we had relatively few men in our sample due to the greater prevalence of depression among women (Hankin et al., 1998), which may have limited our power to detect effects. Thus, it is important that future research replicate this work with more equal sample sizes, which would allow for more statistical power to detect sex effects. Further, we only evaluated a socio-evaluative stressor task, whereas some research with RSA has used an emotion-induction task. Although a socio-evaluative task has been demonstrated to elicit more RSA withdrawal, subsequent studies should conduct research on RSA reactivity using both socio-evaluative stressor and emotion-induction tasks to allow for comparability of study effects. Fourth, we did not examine or observe behaviors related to physiological reactivity, which would allow us to make more direct claims about the behaviors related to blunted RSA reactivity that are contributing to interpersonal stress generation. Further, we only evaluated physiological levels and reactivity at one assessment, and did not

control for all variables that are associated with cardiac activity (e.g., caffeine intake, exercise), which may influence our results. It also would be valuable to examine physiological processes with ambulatory assessment (Schwerdtfeger, & Friedrich-Mai, 2009), which would yield rich information about RSA reactivity to naturally-occurring stressors.

Despite these limitations, the present study has important clinical implications for future research and practice. For one, our preliminary findings indicate that individuals with past subthreshold *or* clinical depression may have similar physiological responses to stress, as well as subsequent risk for daily stress generation and depressive symptoms. Thus, future research should consider examining depression using a more dimensional approach, and examine individual differences within depression to better understand individual risk. Taken together, our findings highlight the importance of resting RSA and RSA reactivity in depression risk. Specifically, our findings suggest that resting RSA and RSA reactivity may contribute specific risk for depression via unique processes. In particular, resting levels of RSA may have a direct impact on affective mood states, and thus, may be a better physiological marker of self- and affective dysregulation. Alternatively, RSA reactivity may have an indirect effect on depression through its influence on interpersonal functioning. Specifically, blunted RSA reactivity prospectively predicted greater interpersonal stress generation, suggesting that these individuals may not appropriately cope or regulate their stress response, thereby inadvertently contributing to stress in their interpersonal relationships. In this sense, RSA reactivity may be a more adequate marker of stress-regulation, particularly related to interpersonal stress. Importantly, these findings highlight the predictive power of resting RSA and RSA

reactivity for daily depressive symptoms, but also indicate that RSA reactivity may contribute to stress generation, which is a mutable risk factor for subsequent depression. Future research is needed to evaluate these processes in the prospective development of depression onset and recurrence, as well as to integrate our findings with other ANS, immune system, and neurobiological indices of depression vulnerability.

CHAPTER 2: SYSTEMATIC LITERATURE REVIEW

Atypical Reactivity of Heart Rate Variability to Stress and Depression: Systematic Review of the Literature and Directions for Future Research

Abstract

Heart rate variability (HRV) has received growing attention in the depression literature, with several recent meta-analyses conducted of studies of resting HRV and depression. However, the role of HRV reactivity to a laboratory-induced stress task in depression has remained less clear. The present review provides a systematic examination of the literature on HRV *reactivity* and depression, including 25 studies of HRV and clinical depression, remitted (or history of) depression, and subthreshold depression (or symptom-level depression) among adults, children, and adolescents. In addition to reviewing the findings of these studies, methodological considerations and conceptual gaps in the literature will be addressed. In particular, we conclude by highlighting the importance of investigating the potential transactional relationship between HRV reactivity and depression and possible mechanisms underlying this relationship.

Keywords: heart rate variability, depression, stress, reactivity, respiratory sinus arrhythmia

Introduction

Major Depressive Disorder (MDD) is one of the most prevalent mental disorders, with current lifetime estimates of 20% of the US population (Kessler et al., 2009). MDD is associated with significant functional impairment and is one of the leading causes of disability worldwide (World Health Organization, 2008). Beyond the personal costs of depression, MDD also has significant societal, financial, and economic costs (Greenberg, Fournier, Sisitsky, Pike, & Kessler, 2015), and is projected to be the second largest disease burden within the next 5 years (Murray & Lopez, 1997). Part of MDD's debilitating effect is due to its high rates of recurrence, with approximately 50% of individuals who recover from MDD likely to have another episode in their lifetime (American Psychiatric Association, 2000) and up to 80% of those with a history of two or more episodes of depression likely to have another recurrence (Burcusa & Iacono, 2007). In addition to clinical depression, subthreshold depression also is associated with similar course and impairment as MDD (Gotlib, Lewinsohn, & Seeley, 1995; Kessler, Zhao, Blazer, & Swartz, 1997), and is predictive of first onset of MDD (van Lang, Ferdinand, & Verhulst, 2007). Given the debilitating effects of MDD and subthreshold depression, considerable research has sought to identify factors that confer risk for the development and maintenance of MDD, which will serve to better identify at-risk individuals and inform personalized prevention and intervention programs.

The occurrence of stressful events is one of the best predictors of MDD, including first onset (Kendler, Karkowski, & Prescott, 1999; Lewinsohn, Allen, Seeley, & Gotlib, 1999; Monroe, Rohde, Seeley, & Lewinsohn, 1999), relapse (Burcusa & Iacono, 2007; Monroe, Roberts, Kupfer, & Frank, 1996), and increases in depressive symptoms (Ge,

Lorenz, Conger, Elder, & Simons, 1994). Given the plethora of research documenting the importance of stress in depression (see Monroe, Slavich, & Georgiadas, 2014, for a review) and the fact that not everyone who experiences stressful events develops depression, there has been an increased focus on elucidating the human psychobiological stress response in depression risk and maintenance. This research has primarily focused on the autonomic nervous system and hypothalamic-pituitary-adrenal (HPA) axis, and more recently, inflammation processes and the immune system. Although an individual's stress response is a complex and coordinated process involving all of these biological components that are important in determining the relationship between stress reactivity and psychopathology (Allen, Kennedy, Cryan, Dinan, & Clarke, 2014; Chida, Hamer, & Steptoe, 2008), the present review exclusively focuses on literature related to the reactivity of the autonomic nervous system, particularly related to heart rate variability (HRV), within the context of depression.

There are a number of reasons why a systematic review of ANS reactivity, particularly HRV, and depression is especially warranted, despite the additional importance of the neuroendocrine and immune systems, and other indices of the ANS response. For one, there are already several comprehensive reviews and meta-analyses of the literature concentrated on the HPA axis response to psychological stressors in laboratory and natural settings (Biondi & Picardi, 1999; Dickerson & Kemeny, 2004; Michaud, Matheson, Kelly, & Anisman, 2008), particularly in relation to depression among adults (Burke, Davis, Otte, & Mohr, 2005), as well as children and adolescents (Lopez- Duran, Kovacs, & George, 2009). Second, although dysregulation of the immune system is at the foreground of emerging research on biological markers of depression (Morey, Boggero, Scott, & Segerstrom, 2015),

there remains a scarcity of research that examines the reactivity of the immune system to laboratory-induced psychological stressors. Thus, a review of this literature will be needed as this research emerges. Third, abnormalities in the autonomic nervous system (ANS) have been identified as important markers of risk for a range of negative health outcomes (Phillips, Ginty, & Hughes, 2013), including cardiovascular disease and depression. Indeed, there are a number of comprehensive reviews and meta-analyses documenting the significant relationship between coronary disease and depression across studies (e.g., Grippo & Johnson, 2009; Van der Kooy et al., 2007; Joynt, Whellan, & O'Conner, 2003), which together are the world's leading causes of mortality and disability (Murray & Lopez, 1997). Further, meta-analyses indicate that subthreshold and clinical depression may actually increase the risk for the onset of coronary heart disease (Rugulies, 2002; Wulsin & Singal, 2003), and identify clinical depression as the most important risk factor for the development of cardiovascular disease beyond the effects of smoking or diabetes (Van der Kooy et al., 2007). Relatedly, abnormalities in the ANS to induced stress, particularly related to cardiac reactivity, have been identified as potential mechanisms linking depression and poor cardiovascular health (Grippo, 2009; Grippo & Johnson, 2009; Taylor, 2010; Thayer & Lane, 2009). Thus, a review more clearly delineating the role of autonomic cardiac reactivity in depression may also provide important information for the treatment and prevention of two serious physical and mental health conditions. Fourth, the brain's control over the ANS, as indexed by cardiac activity, also has been implicated in the immune and endocrine systems (Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012; Thayer & Sternberg, 2010), which may increase the importance of better understanding ANS cardiac reactivity, specifically HRV, in depression. Finally, there are only two comprehensive reviews or meta-analyses on the relationship

between heart rate variability and depression (Kemp et al., 2010; Rottenberg, 2007). Although these important reviews provide support for the role of HRV in depression (Kemp et al., 2010; Rottenberg, 2007), neither review included studies on the *reactivity* of HRV among depressed individuals, which has important implications for understanding how individuals' responses to environmental challenges and stressors relates to depression. Thus, given the burgeoning research in the past few years evaluating physiological stress *reactivity*, particularly related to the polyvagal theory (Porges, 1995, 2007) and Neurovisceral Integration model (Thayer & Lane, 2000), a thorough review of the existing literature is needed to provide better direction for this field.

Accordingly, the present article begins with a brief discussion of the role of the autonomic nervous system in the stress response, with an emphasis on the particular theoretical significance of the various HRV indices that are the focus of this review. From this context, the next section presents a review of the evidence to date on HRV *reactivity* and depression, including research on adults with 1) clinical depression, 2) remitted (or history of) depression, and 3) subthreshold depression (or symptom-level depression). As research also has been conducted among children and adolescents, a separate section is devoted to reviewing ANS reactivity in this population in relation to depressive symptoms and disorders. Then, the paper reviews several important methodological considerations, such as the type of stressor task and study design, and priorities for future research. Finally, the paper concludes by highlighting the importance of investigating the potential transactional relationship between HRV reactivity and depression and potential mechanisms underlying this relationship.

Autonomic Nervous System

The ANS regulates our internal environment and responds to changes in the internal and external environment that require psychological and physiological adaptation, also referred to as *stress* (Monroe, 2008). When an individual experiences stress, the ANS coordinates the mobilization of resources through dynamic interactions of the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) to produce various degrees of physiological arousal. Commonly referred to as the "fight or flight" response, the SNS becomes more dominant and initiates a series of quick physiological responses, such as raising cardiac output and accelerating the heart rate. In contrast, the PNS is dominant during periods of rest (or in the absence of stress) and promotes growth and digestion, and regulates recovery. In this sense, the PNS and SNS often interact as antagonistic processes, such that the PNS decreases as the SNS is activated to heighten arousal, and the PNS modulates SNS activation of the heart and serves to regulate and restore the individual to homeostasis (Berntson et al., 1997; Berntson, Cacioppo, Quigley, & Fabro, 1994). Given that the physiological system typically responds in a dynamic and integrated manner, it has been demonstrated that SNS and PNS can be activated simultaneously (coactivation), deactivated simultaneously (coinhibition), or reciprocally activated (indexed by SNS activation and PNS withdrawal or SNS withdrawal and PNS activation) depending on certain environmental conditions (Berntson et al., 1994). Inasmuch as both the PNS and SNS branches of the ANS may determine patterns of the cardiac stress response to varying degrees among different individuals, simultaneous but separate examination of both SNS and PNS reactivity to stress challenges is necessary to provide a more comprehensive assessment of individual

differences in psychophysiological reactivity (Cacioppo, Uchino, & Berntson, 1994; Hollenstein, McNeely, Eastabrook, Mackey, & Flynn, 2012).

The Heart-Brain Connection: Theoretical Significance of Heart Rate Variability

Importantly, theory and research implicate the brain through its influence on the heart in the extent to which individuals can successfully respond and adapt to environmental challenges and self-regulate (Porges, 1995, 2003a, 2007; Thayer & Lane, 2000). Specifically, the Neurovisceral Integration model (Thayer & Lane, 2000) posits that the ANS is regulated by the central autonomic network in the brain, comprised of multiple neuroanatomical structures such as the medial prefrontal cortex, nucleus ambiguus, and amygdala, which receives input regarding the internal and external environment and accordingly adjusts physiological arousal by transmitting output to the sinoatrial node of the heart, which is the primary "pace maker" of the heart (Appelhans & Luecken, 2008; Berntson et al., 1997). In particular, there has been a lot of focus on the parasympathetic influence on the heart through the vagus nerve, which is the tenth cranial artery (Porges, 1995, 2007). According to the Polyvagal theory (Porges, 1995), vagal control of the heart, commonly referred to in the literature as cardiac vagal control, promotes a decrease in heart rate, and ultimately functions as a vagal "brake" (Porges, 2003; 2007). At rest, the vagal pathway conserves energy or "brakes" cardiac activity, thereby inhibiting the sinoatrial node, slowing heart rate, and lowering blood pressure (PNS dominance).

Environmental challenges or stress typically elicit vagal withdrawal and release of the brakes to respond to changing demands, thereby decreasing control of the heart via the vagus nerve. Individual differences in vagal regulation are assessed by measuring

changes in vagal tone from baseline to levels during a challenging state, with levels either reflecting withdrawal of the vagal brake (marked by decreases from baseline to stress) or augmentation of the vagal brake (marked by increases from baseline to stressor). Release of the vagal "brake" facilitates the activation of the SNS when confronted with stress to mobilize physiological and cognitive resources to effectively manage and cope. However, augmentation of the vagal break slows heart rate and inhibits activation of the SNS. Thus, greater vagal withdrawal in response to stress reflects *greater reactivity* of the PNS and is generally considered to be an adaptive response to stress (Porges, 1995; 2007). Although *exaggerated* reactivity of the SNS is associated with negative health outcomes (Chida et al., 2008), greater SNS reactivity (to a point) is reflective of an adaptive response to stress.

In terms of cardiac function, the heart is dually innervated by both the SNS and PNS. Sympathetic activity is associated with excitatory influences on the heart and results in the acceleration of heart rate, which is reflected in shorter time between heart beats. In contrast, parasympathetic activity inhibits the sinoatrial node and contributes to heart rate deceleration, indexed by longer intervals between heart beats. Because the SNS and PNS rely on different mechanisms to influence the heart, changes in heart rate due to sympathetic activation occur more slowly over several seconds, whereas heart rate variation due to PNS regulation occurs much more quickly in milliseconds (Berntson et al., 1997). This rapid ability of the PNS to modulate cardiac activity makes it highly responsive to changes in the environment. However, the interplay of the sympathetic and parasympathetic (vagal) systems in regulating the variation in time intervals between heart beats is the basis of heart rate variability (HRV). In this sense, HRV reflects the

extent to which the brain and its central autonomic network *can* flexibly respond (basal or resting levels) and adapt to environmental challenges (*reactivity*; Porges, 1995; 2003; 2007; Thayer & Lane, 2000). Thus, HRV *reactivity* (or differences in HRV from resting state to stress challenges) serves as an important index of the ability to self-regulate and *react* to stress in the environment (Porges, 2007; Thayer et al., 2012).

Indices of Heart Rate Variability

As the most commonly studied aspect of ANS control of the heart, particularly within the depression literature, heart rate variability (HRV) deserves special attention. There have been several methods used to quantify HRV levels and fluctuations, including time-based and frequency-based (or spectral analysis) approaches. In general, most methods of calculating HRV use the temporal distance between a sequence of intervals of "normal" beats or spikes in heart beat (termed R-spikes). This beat-to-beat variability can be quantified using an electrocardiogram (ECG). Although a review of these calculations is beyond the scope of the present article, a brief synopsis is presented (for a review, see Xhyeri, Manfrini, Mazzolini, Pizzi, & Bugiardini, 2012). In time-based measures, various calculations of the intervals between beats are used to reflect overall HRV, which reflects both SNS and PNS influence, or HRV specific to the PNS. Of note, the most common time-domain measures are the standard deviation of normal-to-normal beats (SDNN), which measures total HRV, and the root mean square successive differences (RMSSD), which reflects the parasympathetic influence on the heart. Similarly, frequency-based methods reflect differences in the distribution of heart rate at different frequencies from parasympathetic and sympathetic influences. Using power spectral analyses, frequency-based measures can parse out the parasympathetic influences, which dominate at high

frequencies (typically between .15-.40 hertz, or cycles per second), and sympathetic influences, which typically occur at lower frequencies (typically .04-.15 HZ). Thus, high-frequency HRV (HF-HRV) primarily reflects the parasympathetic influence on the heart, and occurs over the frequency range associated with normal respiration. In contrast, low-frequency HRV (LF-HRV) is generally considered an index of both sympathetic and parasympathetic influences on the heart, as well as other non-neuronal factors (Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology, 1996). To counter the contamination of LF-HRV by the PNS, many researchers also evaluate the low to high frequency ratio (LF/HF ratio) to index the extent to which SNS or PNS is reciprocally activated or withdrawn, thus greater reactivity would be reflected by larger increases in LF compared to HF. Although both methods of calculating HRV are deemed appropriate, frequency-based measures are typically considered better for measuring HRV over shorter (5-minute or less) intervals (Xhyheri et al., 2012).

Breathing is an important component to consider when evaluating and measuring heart rate, particularly because breathing air temporarily increases heart rate by blocking the parasympathetic influence on the heart, and breathing out results in a heart rate decrease (Berntson, Cacioppo, & Quigley, 1993). Thus, variability in the heart rate that occurs over the respiratory cycle is called respiratory sinus arrhythmia (RSA; Beauchaine, 2001; Porges, 1995; Rottenberg, 2007; Rottenberg, Clift, Bolden, & Salomon, 2007). Because only PNS cardiac activity occurs quickly enough to be influenced by the respiratory process, RSA is considered to be an index of the parasympathetic influence on the heart (or cardiac vagal control). RSA also can be

computed by using the peak-to-valley technique (Grossman & Taylor, 2007), which computes the difference between the interbeat intervals during inspiration and the maximum interbeat interval during expiration. Thus, RSA has quickly emerged as one of the most investigated measures of ANS cardiac activity and HRV.

It is important to note that time-based HRV (RMSSD), frequency-based HRV (HF-HRV), and RSA are differentially calculated measures to reflect the same process of the parasympathetic influence on the heart or cardiac vagal control (Beauchaine, 2001; Xhyheri et al., 2012). Thus, time-based RMSSD, frequency-based HF-HRV, and RSA are all appropriate measures for reflecting parasympathetic control over the heart. Although none of these measures may be completely accurate in estimating actual cardiac vagal control, they are considered to be important non-invasive measures of ANS activity that reflect more central regulatory processes in the brain (Grossman et al., 2007). These indices are further discussed in terms of *resting* level of HRV (also referred to as baseline, basal, or tonic) and HRV *reactivity* (also referred to as fluctuations/oscillations/phasic) in response to a stressor task.

Heart Rate Variability in the Context of Depression

In recent years, indices of HRV (particularly HF-HRV and RSA, which will be the focus of this section) have received considerable attention in the depression literature. Although resting levels and reactivity of HRV may be correlated with one another, research has demonstrated that these indices reflect different processes, such that resting HRV reflects autonomic flexibility, whereas reactivity of HRV indicates self-regulation and mood state in response to challenges (Beauchaine, 2001; Porges, 1995). In particular, HRV not only reflects physiological regulation (as previously described), but also

cognitive and emotional processes and regulation (Appelhans & Luecken, 2006; Beauchaine, 2001; Bylsma, Morris, & Rottenberg, 2008; Butler, Wilhelm, & Gross, 2006; Kreibig, 2010; Porges, Doussard-Roosevelt, Portales, & Greenspan, 1996; Thayer & Brosschot, 2005; Thayer & Lane, 2009; Thayer et al., 2012). Several studies have demonstrated that individuals with greater levels of resting HRV have greater emotion regulation and responding, as well as cognitive regulation and executive functioning (Appelhans & Luecken, 2006; Thayer & Brosschot, 2005; Hansen, Johnsen, & Thayer, 2003). Further, greater capacity to respond to environmental challenges (i.e., greater RSA reactivity or decreases) is associated with attentional and emotional processes that facilitate adaptive responses to stress (Calkins & Keane, 2004; Porges et al., 1996). In contrast, individuals with lower levels of HRV have been found to have poorer emotion regulation abilities and deficits in attentional control and working memory (Appelhans & Luecken, 2006; Hansen et al., 2003).

Given that depression may be considered a disorder of emotion (Rottenberg, 2005) and also is marked by deficits in emotion regulation, cognitive control, and executive functioning (Bylsma et al., 2008; Gotlib & Joormann, 2010), it should come as no surprise that HRV has garnered interest in depression. Rottenberg (2007) conducted the first thorough review and meta-analysis of the relationship between RSA and depression. Evaluating the effects of RSA and depression among clinically depressed patients, Rottenberg (2007) demonstrated a modest association between RSA levels and depression, such that depressed individuals demonstrated significantly lower resting RSA compared to non-depressed or healthy controls across studies. Although the effect size was smaller than anticipated (d = 0.33, CI = .18-.49), there are several reasons

highlighted by Rottenberg (2007) and others (e.g., Kemp et al., 2010). For one, Rottenberg only reviewed studies that were cross-sectional in nature, which limits the ability to draw conclusions regarding the temporal relationships of RSA and depression. Second, although Rottenberg (2007) corrected for prior studies evaluating over-compromised patients with depression and cardiovascular disease, the reviewed studies included samples that were already clinically depressed and evaluated RSA levels over the course of depression and in response to antidepressant medication. Finally, and most pertinent to the present review, Rottenberg did not actually evaluate the effects of RSA *reactivity* in response to a psychological challenge and depression.

To address several of these gaps, Kemp and colleagues (2010) conducted a meta-analysis of the impact of HRV on depression and included studies that evaluated several indices of HRV (including time domain, HF, LF, LF/HF ratio). Included studies also were required to have unmedicated clinically depressed individuals (MDD) and either 1) an age-matched control group without MDD or 2) reported measures of depression severity among the MDD group, and 3) a pre-and post-treatment comparison of an MDD group. Overall, meta-analysis revealed that depression was associated with reduced HF-HRV (RSA) levels, as well as increases in LF/HF ratio (reflecting reduced HF-HRV), but there was no significant effect for LF-HRV between depressed and non-depressed individuals or on severity of depression. Further, individuals with more severe depression had lower levels of HRV than those with less severe depression. Similar to the meta-analysis conducted by Rottenberg (2007), there was only a relatively small effect size for all measures of HRV, including HF- HRV (d = -.21, CI = -.40 - -02) and LF/HF ratio (d = .66, CI = .20 – 1.13). Although this systematic meta-analysis provides pertinent

information regarding the relationship between multiple HRV indices and depression, this study also did not examine the relationship between HRV reactivity and depression nor did it include samples with remitted depression or individuals with elevated depressive symptoms without clinical depression, which might elucidate the role of HRV as a marker of current depression or vulnerability for depression. Despite these limitations, these reviews indicate the presence of a relationship between reduced HRV and clinical depression, which is consistent with theory that HRV is a marker of physiological sensitivity to the environment, and reflects the ability of the organism to prepare to respond and adapt to stressors and challenges.

The Present Review

Despite research demonstrating that resting HRV levels are correlated with HRV reactivity (Porges et al., 1996; Salomon, 2005), these are distinct constructs that reflect different regulatory processes (Rottenberg, Salomon, Gross, & Gotlib, 2005; Rottenberg, Wilhelm, Gross, & Gotlib, 2003). Specifically, whereas resting levels may reflect the *capacity* to respond, HRV reactivity reflects acute changes in self-regulation and state mood in the physiological response compared to rest. Thus, HRV reactivity reflects vagal withdrawal to facilitate SNS activation, indexing the extent to which individuals are mobilizing physiological and cognitive resources to respond to stress accordingly. As stated previously, healthy individuals typically demonstrate HRV reactivity to induced stress (Beauchaine, 2001; Porges, 2007; Thayer & Lane, 2000). Given the importance of the ANS in regulating physiological responses to environmental challenges and psychosocial stress, and the significant relationship between stressors and depression (Hammen, 2005), individual differences in HRV reactivity to stress may be a significant

marker of depression. However, substantial differences may exist among individuals with current clinical depression, remitted depression, or elevated depressive symptoms, as well as among children, adolescents, and adults. Thus, a critical analysis of the role of HRV reactivity in depression is needed.

Method

In reviewing the literature on heart rate variability (HRV), there is an impressive amount of research that has examined the effects of HRV in psychopathology, as well as various medical conditions. In particular, there is considerable research evaluating resting HRV and reactivity of HRV in psychological disorders that are highly comorbid with depression, specifically anxiety disorders. However, this topic alone warrants a systematic review, and a review and meta-analysis of resting HRV was recently conducted (Chalmers, Quintana, Abbott, & Kemp, 2014; Friedman, 2007), although there is a need to expand this literature to HRV reactivity. There also has been abundant research examining constructs that are implicated in and highly relevant to depression, including positive and negative affect, rumination, and emotion. The latter of which was recently reviewed in relation to ANS reactivity, including HRV variables, in an impressive review of 134 studies spanning over 50 years (Kreibig, 2010). Thus, given the plethora of research that could be included through its connection to depression, the present review focuses solely on studies that included HRV reactivity and only depression.

Peer-reviewed articles published between 1993 and 2015 were located in PsycINFO and MEDLINE with all relevant combinations of the following keywords: depress*, heart rate variability, HRV, respiratory sinus arrhythmia, RSA, vagal, cardiac

vagal control, CVC, cardiac vagal tone, autonomic nervous system, reactivity, cardiac reactivity, cardiovascular reactivity, physiological reactivity, stress reactivity. The year 1993 was selected because this is the date of the first reported study of resting HRV reviewed by Rottenberg (2007), and thus may serve as a marker of the emergence of HRV as a construct of interest in depression. In addition to the conducted database searches, the citation list of each relevant article was examined for additional studies. The inclusion criteria were: 1) measures of HRV *reactivity,* as indexed by any HRV variables calculated using frequency-based measures, time-based measures, and/or respiration, 2) reactivity to a laboratory-based psychological stressor (defined broadly as any mental stressor, including speech task, cognitive task, or sad film clips that took place in a controlled environment), 3) a measure of depression, which could be represented by including a group of individuals with current depression or remitted depression, or any measure of depressive symptoms, and 4) the study was written (or translated) in English. Studies were excluded if: 1) the sample also had a medical condition, which may differentially alter HRV reactivity (e.g., van der Kooy et al., 2007), 2) depression-relevant constructs were examined, but depression was included as a control rather than a primary study variable, 3) the relationship of HRV and depression was examined as a function of treatment effects, or 4) reactivity to a non-mental stressor (such as supine versus resting postural change) was included as the stress task.

Results

Included Studies

The search within the electronic databases PsycINFO and MEDLINE for HRV reactivity in depression revealed a total of 221 studies as of May 2015. These were

reduced to 25 after determining whether the study met inclusion and exclusion criteria by examining the study abstracts or text. Studies were excluded if they examined resting HRV, but not reactivity, did not include a specific depression index but evaluated a depression-related construct, evaluated HRV reactivity in response to a non-psychological stressor, or included treatment effects on HRV reactivity. Of those studies that met both inclusion and exclusion criteria, 18 (72%) were studies of adult samples (over 18), six (42%) examined HRV reactivity in relation to children or adolescents, and one study (4%) examined RSA reactivity in both adults and children (offspring). Thus, the following sections are divided based on studies that included adults and studies that included samples of children and adolescents.

Types of Stress Tasks

There was heterogeneity among studies in the type of stressor task used to elicit stress and HRV reactivity across both adult and youth studies, which included cognitive, social, and emotion-induction tasks. Overall, 12 (48%) studies included a cognitive task, 11 (44%) studies included a social stressor, and 9 (36%) studies included an emotion-induction task, such as a film or guided recall. All studies included a baseline period to allow for habituation and a measure of baseline HRV, which served as the basis of comparison for many studies regarding measures of reactivity. Although most studies included a period of unstructured rest, several studies included rest periods with paced breathing (Bylsma, Salomon, Taylor-Clift, Morris, & Rottenberg, 2014) or participation in a neutral task, such as watching a neutral film clip or neutral reading task (Bylsma et al., 2014; Gordon, Ditto, & D'Antono, 2012). Several studies (24%) included a variety of stressor conditions, with most allowing for a recovery period between tasks. Specifically,

several studies used versions of the Trier Social Stress Test (TSST), which has repeatedly been validated as one of the most reliable stress tests (Allen et al., 2014; Dickerson & Kemeny, 2004; Gunnar, Talge, & Herrera, 2009). The TSST consists of a speech condition and a mental arithmetic task. Surprisingly, only two studies (1%) included both conditions of the TSST (Ahrens et al., 2008; Bylsma et al., 2014).

Cognitive Stressors. The cognitive tasks included several number tasks, including a random number generation in which participants have to orally generate a random series of 100 digits using the numbers 0-9 (Shinba, 2014; Shinba et al., 2008), a calculation task in which the participants have to count aloud backwards by a selected number as quickly and correctly as possible (Ahrens et al., 2008; Ehrenthal, Herrmann-Lingen, Fey, & Schauenburg, 2010; El-Sheikh, Keiley, Erath, & Dyer, 2013; Liang, Lee, Chen, & Chang, 2015), and a parity task in which participants have to decide whether the numbers have the same or different parity (Silvia, Nusbaum, Eddington, Beaty, & Kwapil, 2014). Other cognitive tasks included a mirror star tracing task (MSST), in which participants are required to trace around a star as quickly and accurately as possible while only being allowed to see the mirror image of the star and receiving negative feedback from a loud noise when the stylus was not in contact with the star (Matthews, Nelesen, & Dimsdale, 2005; Rottenberg et al., 2007). Two studies also utilized computer tasks, such as a concentration task (Ahrens et al., 2008), Implicit Association task (Licht et al., 2008), and N-Back Task with increasing levels of difficulty (Nugent, Bain, Thayer, Sollers, & Drevets, 2011)

Social Stressors. Social stressors generally included variations of a speaking task. The most commonly used situation was the speech task in which the participants had to

defend themselves from various offenses, such as being wrongly accused for theft or defending themselves out of a traffic ticket (Ahrens et al., 2008; Bylsma et al., 2014; Cyranowski, Hofkens, Swartz, Salomon, & Gianaros, 2011; Hughes & Stoney, 2000; Rottenberg et al., 2007). Another study included role-playing social tasks, which instructed the participants to provide negative feedback to a hostile or agreeable employee and an unscripted debate on abortion (Gordon et al., 2012), whereas one study conducted interviews to gather information and elicit stress (Licht et al., 2008). Among children, a common social stressor included listening to an audiotape of a negative interaction between a man and women, such as a disagreement over an activity (El-Sheikh, Harger, & Whitson, 2001; El-Sheikh et al., 2013). Other stressors included a "hot topics" discussion with a parent over an interpersonal conflict (Crowell et al., 2014) or over a topic that was mutually rated as stressful by the parent and adolescent, such as household chores (Morgan, Shaw, & Forbes, 2013).

Emotion-Induction Stressors. Emotion-induction films were included as well, because this is also considered to be a form of psychological stress. Most film clips were specifically a sadness-induction (Rottenberg et al., 2003), the most common of which was a film clip from "The Champ" in which a boy is grieving over the death of his father (Pang & Beauchaine, 2013; Rottenberg et al., 2005; Yaroslavsky, Bylsma, Rottenberg, & Kovacs, 2013; Yaroslavsky, Rottenberg, & Kovacs, 2013, 2014). For children, sadness-inducing film clips included the scene from "The Lion King" when the young lion almost gets lost in the Stampede (Gentzler, Santucci, Kovacs, & Fox, 2009; Yaroslavsky et al., 2014). Several other studies included various recall tasks designed to elicit specific emotions. For instance, one study used a relationship-focused guided imagery task to

elicit feelings of love (Cyranowski et al., 2011), which was theorized to increase RSA among individuals during social engagement (Porges, 1995), whereas another study instructed participants to recall anger (Ehrenthal et al., 2010).

Calculation of HRV Reactivity

Interestingly, there also was heterogeneity in the calculation of HRV reactivity across studies. Overall, the majority (14) of studies calculated reactivity by subtracting mean levels during the stressor task or challenge from the resting or baseline levels (Crowell et al., 2014; El-Sheikh et al., 2001; Gentzler et al., 2009; Gordon et al., 2012; Hughes & Stoney, 2000; Liang et al., 2015; Morgan et al., 2013; Pang & Beauchaine, 2013; Rottenberg et al., 2005; Rottenberg et al., 2003; Silvia et al., 2014; Yaroslavsky, Bylsma, et al., 2013; Yaroslavsky, Rottenberg, et al., 2013; Yaroslavsky et al., 2014). Other studies utilized a residualized change score by regressing the average levels from the baseline period to the stressor task phase (Bylsma et al., 2014; Cyranowski et al., 2011). Both of these methods take into account both the initial and task levels and calculate actual difference scores to reflect the extent of reactivity (in various directions). Another method utilized by one set of authors utilized ratio scores of HRV for the stressor to rest, with greater scores indicating greater reactivity during the challenge (Shinba et al., 2008; 2014). Finally, several studies have examined group differences using ANOVAs using group (depression status) by study phase (baseline vs. task), which analyzes the effect of HRV across study phase by depression group (Ahrens et al., 2008; Ehrenthal et al., 2010; Licht et al., 2008; Matthews et al., 2005; Nugent et al., 2011; Rottenberg et al., 2007). Only one study examined absolute levels of reactivity, controlling for initial levels (El-Sheikh et al., 2013).

Adult studies of HRV reactivity to a psychological stressor and depression

Current Depression. Of the 19 studies examining HRV reactivity in depression among adults, 10 of these specifically included a sample of adults with current MDD (Bylsma et al., 2014; Cyranowski et al., 2011; Ehrenthal et al., 2010; Liang et al., 2015; Licht et al., 2008; Nugent et al., 2011; Rottenberg et al., 2003; Rottenberg et al., 2005; Rottenberg et al., 2007; Shinba et al., 2014; Table 6). These studies predominantly examined the effects of RSA or HF-HRV reactivity in individuals diagnosed with MDD versus a control (healthy) group (Bylsma et al., 2014; Cyranowski et al., 2011; Ehrenthal et al., 2010; Rottenberg et al., 2003; Rottenberg et al., 2007) and four of these included other indices of HRV, such as LF-HRV and LF/HF ratio, in MDD versus control groups (Liang et al., 2015; Licht et al., 2008; Nugent et al., 2011; Shinba et al., 2014). Overall, the majority of these studies found a significant effect of HRV reactivity by group status, such that currently depressed individuals demonstrated *blunted* RSA withdrawal (reactivity) to the stressor conditions, whereas their non-depressed counterparts experienced the expected RSA decrease (or withdrawal) during the stressor task (Bylsma et al., 2014; Cyranowski et al., 2011; Ehrenthal et al., 2010; Liang et al., 2015; Licht et al., 2008; Rottenberg et al., 2003; 2007; Shinba et al., 2014). This *attenuated* HRV reactivity seems to be more consistent with a more disengaged or passive physiological response, rather than mobilizing the resources necessary to adapt or appropriately respond and cope with the environmental challenge.

In one of the first studies comparing RSA reactivity among depressed individuals to controls, Rottenberg and colleagues (2007) found that the healthy individuals demonstrated significant RSA decreases during the stressor tasks (as expected), but the

Table 6. Adult Studies of HRV Reactivity in Current Depression

Authors	Year	N	N (% MDD)	N (% Female	Mean Age	HRV	Comparison	Stressor Task
Bylsma et al.*	2014	119	49 (43%)	89 (75%)	29.96	RSA	Control rMDD (N = 24)	Social
Cyranowski et al.	2011	30	15 (50%)	15 (100%)	29.83	RSA	Control	Social
Ehrenthal et al.	2010	50	25 (50%)	34 (68%)	27.62	HF	Control	Cognitive
Liang et al.	2015	210	160 (76%)	0 (0%)	24.84	HF LF LF/HF	Control	Cognitive
Licht et al.*	2008	2,373	1,075 (45%)	1,585 (66.8%)	41.80	SDNN	Control rMDD (N = 774)	Social
Nugent et al.	2011	17	10 (59%)	17 (100%)	----	RSA HF LF LF/HF	Control	Cognitive Cognitive
Rottenberg et al.	2003	56	25 (45%)	56 (100%)	32.70	RSA	Control	Emotion
Rottenberg et al.	2005	55	55 (100%)	37 (67%)	33.94	RSA	N/A	Emotion
Rottenberg et al.	2007	50	25 (50%)	37 (74%)	31.66	RSA	Control	Social Cognitive
Shinba et al.	2014	69	22 (32%)	38 (55%)	40.32	HF LF/HF	Control	Cognitive

Note. * = Studies that are also included in the remitted depression section; MDD = Major Depressive Disorder; HRV = Heart Rate Variability; RSA = Respiratory Sinus Arrhythmia; HF = High Frequency; LF = Low Frequency; SDNN = standard deviation of normal-to-normal beats; N/A = Not applicable.

MDD group did not experience RSA decreases during the speech task or mirror-tracing task. Other studies have similarly demonstrated that the MDD group had blunted reactivity to cognitive and emotion-induction stressors (Shinba et al., 2014; Ehrenthal et al., 2010; Liang et al., 2015), as well as a speech stressor (Bylsma et al., 2014). In addition, Rottenberg and colleagues (2003) demonstrated that depressed individuals had a lack of RSA reactivity during a sad film that evoked crying, whereas nondepressed individuals (particularly those who cried) experienced greater RSA reactivity. Further, Cyranowski and colleagues (2011) found evidence that depressed women demonstrated lower RSA during an emotion-induction of affection (love/infatuation), whereas healthy women showed the expected increase. In contrast, depressed women with a trauma history showed blunted RSA levels during the speech stress condition compared with nondepressed women and women with little to no trauma history. Interestingly, two other studies demonstrated the complexity of RSA reactivity, such that the MDD group actually experienced *increases* in RSA (or RSA amplification) following the stressors, which was surprising given theory that the vagal brake should be withdrawn during environmental challenge and not amplified (as an increase would demonstrate; Rottenberg et al., 2007; Liang et al., 2015). However, amplification of HF-HRV could similarly result in less activation of the sympathetic nervous system, as the SNS would be inhibited by the vagal brake, and reflect a poorer response to environmental challenge. Further, within-person increases in HF-HRV during stress among depressed individuals may reflect a need to engage in greater self-regulatory efforts to manage negative emotions, such as emotional suppression or reappraisal (Butler et al., 2006). To date, only one study did not indicate any difference between the depressed and nondepressed group

during the mental stressor, but there was evidence of blunted reactivity in HF HRV and LF/HF ratio during the non-mental stressor (e.g., motor task; Nugent et al., 2011), which supports the notion of differential reactivity among individuals with current depression.

Although most studies have solely evaluated RSA or HF-HRV, four studies did examine the reactivity of LF/HF ratio and LF effects in depression. Findings in regard to these measures were mixed. Shinba and colleagues (2014) did not report the effects of LF- HRV, but did find evidence for blunted reactivity for the LF/HR ratio among depressed individuals compared to nondepressed controls in response to a cognitive stressor. Similar to the findings for HF-HRV, Nugent and colleagues (2011) indicated that the depressed group displayed blunted LF/HF ratio in response to a motor task, but not to the cognitive stressor. There were no significant differences between groups in the LF-HRV reactivity. Further, Licht and colleagues (2008) demonstrated a lower total HRV (as measured by SDNN in time-based calculations) among depressed individuals compared to controls during the task conditions, although these results disappeared after controlling for antidepressant medication use. However, the results by Liang and colleagues (2015) present a more complicated picture of HRV reactivity. Specifically, there were no within-group differences for depressed and nondepressed groups from rest to the stressor task. However, the first-time depressed individuals experienced decreases in LF-HRV and the LF/HF ratio, whereas the control group had *increases* in LF-HRV and LF/HF ratio reactivity to the cognitive stressor task. Similar to the HF-HRV findings in this study (Liang et al., 2015), these findings suggest neither an enhanced or attenuated reactivity to the stressor, but rather a completely different trend of HRV reactivity to stress between depressed and nondepressed groups.

Only one study that included a depressed group examined HRV reactivity in depressed individuals over time (Rottenberg et al., 2005). This study examined RSA reactivity to a sad film as a predictor of longitudinal depression outcome, and found that RSA reactivity predicted depression status (recovered or still depressed) at a six-month follow-up visit. Specifically, individuals with greater RSA reactivity or withdrawal to a sad film, but not an anger or amusement film, were more likely to be recovered and no longer depressed six-months later, whereas those with *blunted* RSA reactivity were more likely to still be depressed. Although this study did not compare currently depressed individuals to a control group, it highlights the importance of RSA reactivity in predicting longitudinal outcomes among depressed individuals. Of note, this was the only study to examine HRV reactivity in current depression over a follow-up period and did not examine the correlation between HRV reactivity and depression at one study visit (as found in the previously discussed studies).

Remitted Depression. In total, six studies examined the effects of HRV reactivity among individuals with remitted depression compared to healthy controls with mixed findings (Ahrens et al., 2008; Bylsma et al., 2014; Licht et al., 2008; Yaroslavsky, Bylsma, et al., 2013; Yaroslavsky, Rottenberg, et al., 2013; Yaroslavsky et al., 2014; Table 7). Surprisingly, only one study found a significant difference in RSA (HF) HRV reactivity between formerly depressed and control groups (Licht et al., 2008). In a large cross-sectional depression cohort study in the Netherlands including 524 controls and 774 individuals with remitted depression, Licht and colleagues (2008) found that those with remitted depression exhibited blunted RSA and total HRV reactivity to the stressor

Table 7. Adult Studies of HRV Reactivity in Remitted Depression

Authors	Year	N	N (% rMDD)	Comparison	N (%) Female	Mean Age	HRV	Stressor Task
Ahrens et al.	2008	42	22 (52%)	Control	42 (100%)	52.52	HF LF LF/HF	Social Cognitive
Yaroslavsky, Bylsma et al.*	2013	149	74 (50%)	Control	149 (100%)	27.95	RSA	Emotion
Yaroslavsky, Rottenberg et al.	2013	206	114 (55%)	Control	152 (74%)	27.34	RSA	Emotion
Yaroslavsky et al.	2014	70	27 (39%)	Control	70 (100%)	30.01	RSA	Emotion

Note. * = Study includes both remitted depression and measures depressive symptoms as well; rMDD = Remitted Major Depressive Disorder; HRV = Heart Rate Variability; RSA = Respiratory Sinus Arrhythmia; HF = High Frequency; LF = Low Frequency.

condition. These results held even after accounting for age, sex, and numerous lifestyle indicators (smoking, CVD, alcohol, heart medication, body mass index, physical activity). However, other studies have failed to detect significant differences in HRV reactivity between those with and without remitted depression to speech, cognitive, or emotion stressors (Ahrens et al., 2008; Bylsma et al., 2014; Yaroslavsky, Bylsma, et al., 2013; Yaroslavsky, Rottenberg, et al., 2013; Rottenberg et al., 2014). For instance, in three studies, Yaroslavsky and colleagues examined RSA reactivity among adults with juvenile-onset depression (by age 14) compared to controls with no psychiatric diagnosis in response to an emotion-induction film clip. In all three studies, RSA reactivity alone did not significantly predict depression status, but was associated with remitted depression status and depressive severity among those with remitted depression only in interaction with resting RSA. Specifically, greater RSA withdrawal was protective against depression in the context of higher resting RSA, but there was no effect of low resting RSA levels (Yaroslavsky, Bylsma, et al., 2013, Yaroslavsky, Rottenberg, et al., 2013). Further, Yaroslavsky, Bylsma, and colleagues (2013) also found that women with greater RSA reactivity (decreases in RSA) and high resting RSA were less likely to report maladaptive repair responses (i.e. mood regulation strategies that prolong or amplify distress) and depressive symptoms. However, those with "sub-optimal (atypical) RSA patterns," including high resting RSA and increases in RSA to stress or low resting RSA and greater RSA withdrawal, were more likely to report maladaptive repair responses and depressive symptoms. These findings highlight the potential utility of combining resting and reactivity RSA indices. As previously mentioned, only one study examined other

HRV indices and did not find any significant difference between those with and without a history of depression (Bylsma et al., 2014).

Current versus Remitted Depression. Importantly, research also has evaluated whether HRV reactivity is a state-dependent marker of depression. However, only three studies have compared a group of individuals with remitted MDD to a current MDD group to evaluate whether HRV reactivity is blunted only among those with current depression or also among those with any former history of depression (Bylsma et al., 2014; Licht et al., 2008; Yaroslavsky et al., 2014; Table 6). These studies yielded inconsistent findings, with the study by Licht and colleagues (2008) finding no significant differences between remitted MDD and current MDD groups in response to the stressor in total HRV or HF-HRV, but found that both groups did significantly differ from the control group. Similarly, Yaroslavsky and colleagues (2014) did not find evidence that RSA reactivity significantly predicted current versus remitted depression. RSA reactivity in combination with resting RSA also did not significantly differentiate current and remitted depressed groups. This effect was such that both current and remitted MDD groups demonstrated atypical RSA patterns (described previously), which were significantly different than controls. These studies suggest that current and remitted depressed groups may have similar HRV reactivity. However, Bylsma and colleagues (2014) found that only those with current MDD, and not those with a history of MDD, demonstrated blunted RSA reactivity to the speech stressor task compared to the control group.

Depressive symptoms. Six studies have moved beyond clinical depression to evaluate whether HRV reactivity is associated with increased depressive symptoms

(Gordon et al., 2012; Hughes & Stoney, 2000; Matthews et al., 2005; Shinba et al., 2008; Silvia et al., 2014; Yaroslavsky, Bylsma, et al., 2013; Table 8), which may indicate that HRV reactivity is not a *scar* resulting from a depressed episode or dependent on depressed state, but perhaps a marker of depression risk. Similar to the aforementioned studies with remitted and current depression, the findings are mixed regarding whether blunted or amplified HRV reactivity is associated with depressive symptoms (Hughes & Stoney, 2000; Shinba, 2008; Yaroslavsky, Rottenberg, et al., 2013), if at all. Three studies have failed to find evidence that HRV reactivity, including HF-HRV, LF-HRV, and time-based measures of HRV [RMSSD], predicted heightened depressive symptoms to stressors that were either cognitive (Matthews et al., 2005; Silvia et al., 2014) or social (Gordon et al., 2012). On the contrary, Hughes and Stoney (2000) found that relatively healthy college students with greater depressive symptoms exhibited greater *decreases* in HF-HRV during a speech task, which provides evidence that greater RSA withdrawal is associated with depression. However, Yaroslavsky, Rottenberg, and colleagues (2013) found that greater *increases* in HF-HRV (RSA amplification) predicted elevated depressive symptoms in response to the sad film, controlling for prior depression history. Still, more consistent with the findings of current depression, Shinba and colleagues (2008) demonstrated that individuals with reduced reactivity to a cognitive stressor were more likely to have greater depressive symptoms.

Given the paucity of research and the highly inconsistent findings to date, more research is needed to determine the relationship between HRV reactivity and depressive symptoms among adults. In particular, whereas studies evaluating group differences between current and remitted depression and healthy controls utilized more consistent

Table 8. Adult Studies of HRV Reactivity in Depressive Symptoms

Authors	Year	N	N (%) Female	Mean Age	HRV	Stressor Task
Gordon et al.	2012	199	118(59%)	41.10	HF LF/HF ratio	Social
Hughes & Stoney	2000	53	28 (53%)	18.70	HF	Cognitive
Matthews	2005	91	45 (49%)	18-50*	RSA	Emotion
Shinba et al.	2008	43	12 (28%)	31.10	HF LF/HF	Cognitive
Silvia et al.	2013	131	85 (65%)	19.37	RSA	Cognitive
Yaroslavsky, Bylsma et al.	2013	70	70 (100%)	30.01	RSA	Emotion

Note. * = No mean age given; HRV = Heart Rate Variability; RSA = Respiratory Sinus Arrhythmia; HF = High Frequency; LF = Low Frequency.

sets of criteria (such as diagnostic criteria) as the basis of study inclusion, the samples included in the studies investigating depressive symptoms were heterogeneous. Specifically, three studies included undergraduate samples of young adults (Hughes & Stoney, 2000; Matthews et al., 2005; Silvia et al., 2014), one study included a community sample of adults across ages 18-65 (Gordon et al., 2012), one study included a samplerecruited from a business company (Shinba et al., 2014), and one study recruited those with remitted depression and healthy controls (but collapsed across studies for depressive symptom analyses; Yaroslavsky, Rottenberg, et al., 2013). Further, four studies screened for the presence or absence of psychiatric disorders (Gordon et al., 2012; Matthews et al., 2005; Shinba et al., 2008; Yaroslavsky, Rottenberg, et al., 2013), whereas two did not screen out individuals with other psychiatric disorders (Hughes & Stoney, 2000; Silvia et al., 2014). It is also unclear to what extent these studies generally included samples with clinically elevated depressive symptoms versus lower levels of symptomatology (Gordon et al., 2012). Given the wide variation of samples included, it is difficult to draw conclusions regarding the role of HRV reactivity in predicting subthreshold depression. Importantly, none of these symptom-level studies evaluated the prospective prediction of depressive symptoms, which will be important in differentiating whether HRV reactivity is a consequence of depression or potentially a marker of vulnerability to future depression.

Child and adolescent studies of HRV reactivity to a psychological stressor and depression

Given the focus of the polyvagal theory on self- and emotion regulation (Porges, 2007), an abundance of research has examined RSA in relation to children's development

and functioning. A review of this literature is beyond the scope of the present paper, and has been reviewed in depth elsewhere (Graziano & Derefinko, 2013); however, fewer studies have examined children's and adolescents' HRV reactivity to laboratory-based stressors in relation to depression risk. Examining markers of depression risk is important for a multitude of reasons, such as early identification of those at risk to improve prevention and intervention efforts, given that depressive disorders drastically increase across the adolescent years (Hankin et al., 1998). Further, better understanding the development of HRV reactivity in depression risk during younger ages may provide useful information regarding the temporal relationships between these processes. To date, only seven studies have evaluated HRV reactivity in depression among children (El-Sheikh et al., 2001; 2013; Gentzler et al., 2009; Pang & Beauchaine, 2013; Yaroslavsky et al., 2014) and adolescents (Crowell et al., 2014; Morgan et al., 2013). Although there are additional studies that have examined internalizing symptoms, it is important to differentiate these studies to better parse out the effects that may or may not be specific to depressive symptoms. Further, Graziano and colleagues (2013) recently reviewed the association of RSA reactivity with internalizing symptoms and found that greater RSA withdrawal or reactivity predicted fewer internalizing symptoms across studies (d = .16), suggesting that blunted reactivity may be associated with internalizing symptoms among youth. Thus, only findings that specifically included measures of depressive symptoms or evaluated group differences with clinical depression were included in this review. All of these studies focused exclusively on RSA (or HF/HRV), and thus, only findings regarding this HRV index will be reviewed. In contrast to adult studies, several of these

studies included a longitudinal design and examined other components of self-regulation or behavior in the hypothesized relationship between RSA reactivity and depression.

Depressive Symptoms or Disorders. Seven studies evaluated RSA reactivity among children and adolescents as a predictor of clinical depression or depressive symptoms (Crowell et al., 2014; El Sheikh et al., 2001; 2013; Gentzler et al. 2009; Morgan et al., 2013; Pang & Beauchaine, 2013; Yaroslavsky et al., 2014; Table 9). These studies yielded inconsistent findings regarding the main effects of RSA reactivity on depression, with only two studies finding significant main effects (Gentzler et al., 2009; Pang & Beauchaine, 2013). However, the direction of these effects was not consistent between the studies, such that Pang and colleagues (2013) found that children with clinical depression experienced greater RSA reactivity (e.g., greater decreases in RSA) in response to the sad film clip compared to those with only conduct disorder or healthy controls. However, Gentzler and colleagues (2009) found that children with greater depressive symptoms had reduced RSA withdrawal (or reactivity) to a sad film clip. Interestingly, this was not mediated by maladaptive emotion regulation, which was unrelated to RSA reactivity (Gentzler et al., 2009).

The remaining five studies evaluated RSA reactivity in interaction with verbal marital conflict (El-Sheikh et al., 2001; 2013), other physiological measures (El-Sheikh et al., 2013; Yaroslavsky et al., 2014) and behavior (Crowell et al., 2014; Morgan et al., 2013). Specifically, two studies expanded on the RSA reactivity - depression link by evaluating the interaction between physiological and behavioral risk factors in predicting depression. In a three-wave longitudinal study of 160 at-risk boys from ages 9-10 through

Table 9. Child and Adolescent Studies of HRV Reactivity in Depression

Authors	Year	N	N (% MDD)	Comparison	N (%) Female	Mean Age	HRV	Stressor Task
Crowell et al.	2014	75	50 (75%)	Control	75 (100%)	16.10	RSA	Social
El-Sheikh et al.	2001	75	N/A	N/A	36 (48%)	9.90	RSA	Social
El-Sheikh et al.	2013	251	N/A	N/A	128 (51%)	8.23	RSA	Social
Gentzler et al.	2009	65	N/A	N/A	30 (46%)	7.93	RSA	Emotion
Morgan et al.	2013	160	1.3% (age 12) 8.6% (age 15)	N/A	0 (0%)	---	RSA	Social
Pang & Beauchaine	2013		28 (14%)	CD MDD and CD Control	----	9.90	RSA	Emotion
Yaroslavsky et al.	2014	97	48 (50%)*	Low risk	51 (53%)	6.70	RSA	Emotion

Note. * = Percent high-risk youth based on maternal history of depression. MDD = Major Depressive Disorder; HRV = Heart Rate Variability; N/A = Not applicable; CD = Conduct Disorder.

age 15, Morgan and colleagues (2013) found that RSA reactivity at age 12 did not predict depressive symptoms at ages 12 or 15. However, the interaction between RSA reactivity and social withdrawal predicted depressive symptoms at age 15, such that boys who had less RSA reactivity in a "hot topics" discussion with parents and higher social withdrawal reported the greatest levels of depressive symptoms in mid-adolescence. On the contrary, Crowell and colleagues (2014) found that depressed adolescent girls who were more aversive during a 10-minute interaction task with their mother were more physiologically dysregulated and experienced more moment-to-moment decreases in RSA (or greater RSA reactivity) during the task. This was not the case for depressed teens who were less aversive during the interaction task or those who were not depressed, suggesting a unique concordance between physiological and behavioral dysregulation among the adolescent girls who were depressed. In addition, the first study conducted by El-Sheikh and colleagues (2001) in relation to depressive symptoms found that RSA reactivity to a social stressor (listening to audiotaped segments of adults arguing) did not significantly predict depressive symptoms or buffer the effects of marital conflict on child outcomes. However, in a subsequent study, El-Sheikh and colleagues (2013) found that girls with higher RSA and lower sympathetic response during the stressor (controlling for initial levels) experienced the highest levels of depressive symptoms from middle to late childhood, but only if they came from a home in which there were higher levels of marital conflict. These authors suggest that greater RSA reactivity may be generally adaptive for responding to stress; however, it may be important to consider the context or environment to which these youth are generally exposed. Thus, greater reactivity among youth exposed to more chronic stressors may be more maladaptive for depression

outcomes. Furthering the examination of environment and context, Yaroslavsky and colleagues (2014) evaluated RSA reactivity and depressive symptoms among 97 children of either juvenile-onset depression or healthy mothers across middle childhood to adolescence. Results indicated that RSA reactivity did not predict depressive trajectories, but youth with atypical patterns of RSA, such as low resting RSA and greater RSA withdrawal and high resting RSA and RSA augmentation, experienced the greatest increases in depressive symptoms across adolescence. In addition, there was concordance between mothers' and offsprings' RSA reactivity, and atypical RSA patterns were more prevalent among youth with formerly depressed mothers. These findings suggest that physiological regulation and reactivity to stress may be one mechanism of familial transmission of depression. Further, the findings by Yaroslavsky and colleagues (2014) may provide more insight into the inconsistent findings of prior studies among children and adolescents, and even adults.

Discussion

Overall, the present review highlights the current research on individual differences in *reactivity* of heart rate variability (HRV) in response to laboratory-based stressors in current and remitted clinical depression and depressive symptoms among studies of adults and youth. Given the focus of theories on cardiac vagal control and regulation (Porges, 1995; Thayer & Lane, 2000), most research has focused on the non-invasive measures of the parasympathetic system and vagal withdrawal, which are quantified as high-frequency (HF- HRV) or respiratory sinus arrhythmia (RSA), in depression. In short, these findings confirm a significant role of the physiological stress response, specifically RSA (or HF-HRV), such that individuals with clinical depression

or elevated depressive symptoms demonstrate atypical or dysregulated HRV responses to stressors. Research has been less thorough in the investigation of other HRV indices, such as LF-HRV and LF/HR HRV, preventing conclusions regarding these measures. Although two prior meta-analyses of HRV and depression found that depressed individuals demonstrated lower HRV levels than controls (Kemp et al., 2010; Rottenberg, 2007), the present review highlights the complexities of HRV reactivity in depression.

Among adult studies, the most consistent associations of HRV reactivity with depression appear to be for current depression, with the majority of studies (70%) finding that depressed individuals demonstrated blunted RSA reactivity compared to either a healthy control group or when predicting poorer depression recovery. However, several of these studies did indicate that amplified RSA (increases in RSA) to the stressor also were maladaptive. Findings among those with remitted depression were somewhat less clear, with the majority of studies (83%) failing to find significant group differences between those with remitted depression and healthy controls when investigating HRV reactivity main effects, which suggests that atypical HRV reactivity may be state dependent on current depression. In addition, only half of the studies investigating subthreshold depression found a significant effect of HRV reactivity predicting elevated depressive symptoms, with these studies finding three different patterns of risk (blunted reactivity, RSA amplification, or greater RSA withdrawal). However, a series of studies may shed some light on the variability of HRV findings, finding that RSA withdrawal (decreases) or amplification (increases) may depend on resting levels of HRV, such that atypical patterns significantly differentiated those with current and remitted depression compared to healthy controls and predict greater depressive symptoms (Yaroslavsky,

Bylsma, et al., 2013, Yaroslavsky, Rottenberg, & Kovacs, 2013; 2014). Although the potential utility of combining RSA indices remains to be replicated in additional samples, it may be important to consider both resting HRV and *reactivity* of HRV in depression risk.

Empirical research on HRV reactivity associated with depression among children and adolescents yields similarly inconsistent findings, with only two (28.6%) studies demonstrating main effects of RSA reactivity, but in different directions (greater RSA reactivity and blunted reactivity), among clinically depressed adolescents and children with elevated depressive symptoms. However, the majority of youth studies of HRV reactivity and depression included potential moderators of this relationship, such as other physiological measures, as well as environmental and behavioral influences, and 80% of these studies found significant effects. Results revealed that greater RSA reactivity (when in combination with lower sympathetic reactivity and greater marital conflict or with greater aversive behavior) predicted depression, whereas boys with greater social withdrawal and blunted RSA reactivity experienced the greatest depressive symptoms over time. Similar to the findings in adults, another study found that greater RSA reactivity (withdrawal) and greater RSA amplification both predicted elevated depressive symptoms depending on resting levels of RSA, which may explain some of the discordant findings related to HRV reactivity in children and adolescents. Further, examining potential moderators, including indices of HRV and ANS reactivity, may provide greater insight into discrepancies across findings in the association between HRV reactivity and depression. Of note, no known study of youth depression and HRV

included other indices of HRV, such as LF or LF/HF ratio, so it is unclear whether these indices of HRV reactivity have a role in depression among youth.

Importantly, the majority of this research has been conducted in the past decade, which highlights the evolving focus of the field on underlying biological processes in the etiological foundations of psychopathology. Given the relatively young nature of this research, there are a number of methodological considerations to be discussed, as well as important avenues for future research. Thus, we conclude by proposing potential mechanisms in need of investigation.

Stressor Task. After reviewing a total of 25 studies, it should become clear that there is wide variability in the types of stressor task used to induce psychological stress among studies examining HRV reactivity in depression. Surprisingly, results did not appear to differ based on whether the study design included cognitive, social, or emotion-induction tasks. However, it does make it incredibly difficult to draw firm conclusions regarding the effect of HRV reactivity in depression as different types of stressors may elicit unique physiological responses. For instance, a laboratory-based stressor that cues safety or positive social engagement should be associated with the activation of the vagal brake (or increases in RSA) according to polyvagal theory (Porges, 1995), whereas a laboratory-based stressor that cues threat should elicit vagal withdrawal or decreases in RSA, HF-HRV, and increases in LF-HRV and LF/HF ratio of HRV. Specifically, cognitive stressors, such as mental arithmetic or the mirror star tracing task, are performance stressors that are recognized as active and self-relevant threat stressors (Schwerdtfeger & Rosenkaimer, 2011), whereas social stressors, such as speeches, are active and social-evaluative stressors. In contrast, emotion-inductions are passive

stressors designed to elicit specific emotions, such as sad mood in the case of most sad film clips included in the present review. In general, more active tasks, such as cognitive and speech stressors, have been found to elicit RSA withdrawal in healthy samples, although some individuals have exhibited increases in RSA during these tasks (Berntson, Cacioppo, & Quigley, 1991; Berntson et al., 1994; Cacioppo et al., 1994). Although there may be trends of how individuals may typically respond to these stressors and the relative stability of these responses over time (Kamarck, Jennings, Pogue-Geile, & Manuck, 1994; Salomon, 2005), there is a reliability issue in the extent to which a given challenge will produce HRV responses among individuals, particularly among those vulnerable to depression. Even among the speech tasks, there is also wide variability, with some tasks requiring participants to defend themselves to a mock judge or to have heated discussions with others, which also may elicit different levels of stress among different individuals, particularly depending on personal experience and environmental context. Although social stressors may pose additional challenges if there is an evaluative component, such as potential interactions with age, race, or gender of the experimenter, these may be more similar to the stressors individuals are exposed to in daily life. Only 37% (N = 7) of adult studies included some component of a psychosocial stress task, whereas almost all studies of youth incorporated a social component in the stressor task. Evaluating physiological responses to tasks that involve a social-evaluative component may be important in depression, given research that social stressors may confer greatest risk for depression (Hammen, 2005). Surprisingly, the interpersonal tasks for youth seem to be more reflective of daily life stressors, such as fights or discussions with family members, rather than defending oneself against a crime. Thus, a more comprehensive study of

multiple stressor tasks using the same sample will enhance our understanding of physiological reactivity in depression and may explain some of the inconsistencies in the literature to date.

Further, given the concern that laboratory-based stressors may not be ecologically valid and reflect actual responses to real life stressors, there is a need for ambulatory studies of HRV reactivity in depression. To date, no known study has evaluated the effects of HRV in response to naturally-occurring stressors in the context of depression. However, a recent study examined ambulatory heart rate variability, social interactions, and symptoms of depression (Schwerdtfeger & Friedrich-Mai, 2009). These findings suggested that lower HRV (specifically RMSSD, the time-based measure of HF-HRV/RSA) marginally predicted daily depressive mood. However, there was a significant interaction between ambulatory HRV and social interactions, such that adults with greater depressive symptoms exhibited lower HRV when they were alone, but showed increasing HRV when they were engaged in social interactions with close friends, partners, or family members. However, individuals with lower depressive symptoms showed the opposite trend (Schwerdtfeger & Friedrich-Mai, 2009). Thus, examining HRV reactivity to both laboratory-based stressors and daily life stressors in the context of depression may be an important extension of current research and allow for more fine-grained examinations of HRV reactivity to a variety of stressors and depressed mood.

Longitudinal Study Design. Perhaps one of the most glaring issues of study designs included in the current review is the lack of longitudinal studies, particularly among adult samples. With the exception of one adult study of depression recovery, all

adult studies were correlational in nature and did not longitudinally examine the effects of HRV reactivity on depression. One possibility for future research is to examine the effects of idiographic (or within-person) changes over time in HRV reactivity across depression symptoms and diagnoses (e.g., prior to first-onset of depression, during depressive episode, and following depression remission). This would better elucidate the within-person changes of HRV reactivity and depression rather than relying on between-person differences in reactivity on the basis of diagnosis alone, inasmuch as there is considerable heterogeneity in depression (Goldberg, 2011). Further, it would be particularly informative to examine HRV reactivity as a potential marker of risk for depression among vulnerable individuals, as indicated by multiple indices of risk such as genetic risk, familial history, or even prior history of depression. In particular, studies examining individuals who are at risk for future depression (both first onset and recurrence) would better inform whether atypical HRV reactivity is a scar of depression, state dependent on current depression or elevated symptoms, or contributor to future depression risk.

Developmental Influences in Study Design. Among children and adolescents, longitudinal studies are more common, which represent a significant contribution to our understanding of HRV reactivity over time, as well as its effects on depression. However, there are a number of developmental influences on HRV reactivity that are in need of further examination. For one, there are significant maturational changes in both respiration and heart rate (Bar-Haim, Marshall, & Fox, 2000), with several studies demonstrating that there are normative developmental increases in RSA reactivity across childhood and adolescence (Hinnant, Elmore-Staton, & El-Sheikh, 2011; Pang &

Beauchaine, 2013). Yet, another study demonstrated that LF-HRV reactivity did not change from mid-adolescence to emerging adulthood (ages 12 - 23), but HF-HRV reactivity decreased across this developmental period (Hollenstein et al., 2012). Although patterns of HRV reactivity may remain somewhat stable over time (Hinnant et al., 2011; Salomon, 2005), there is also considerable evidence that the development of the stress response is continuing (Hollenstein et al., 2012; Romeo, 2010) and certain environmental experiences may influence its development (e.g., Evans et al., 2013; see below for more detail). In addition, there also are changes in the responsiveness of the physiological system to different stressors from childhood to adolescence (Obradovic, 2012; Stroud et al., 2009; Sumter, Bokhorst, Miers, Van Pelt, & Westenberg, 2010), such that HRV reactivity to social stressors may be particularly important in depression risk during adolescence (Burnett, Thompson, Bird, & Blakemore, 2011). Further, the biological and pubertal changes during adolescence alter physiological responses to stress both directly and indirectly through its effects on the prefrontal cortex (Gunnar & Vazquez, 2006; (Spear, 2009). Thus, it remains unclear to what extent HRV reactivity to stress during childhood may confer risk to depression in adolescence, and similarly, the extent to which HRV reactivity in adolescence may contribute to the development of depressive disorders during this vulnerable period or even into adulthood. Therefore, longitudinal studies of HRV reactivity to various stressors across multiple developmental periods would better inform the stability and variability of HRV reactivity, as well as lead to better understanding of when different atypical patterns of HRV reactivity confer greatest risk for depression.

Sex differences. Given that sex differences have been observed in HRV (Chambers & Allen, 2007; Thayer, Smith, Rossy, Sollers, & Friedman, 1998) and the greater depression rates found among women (Hankin et al., 1998), it is surprising that few studies have evaluated sex differences in HRV reactivity in depression. At rest, women generally have demonstrated larger resting levels of RSA than men (Chambers & Allen, 2007; Thayer et al., 1998) and larger decreases in RSA to speech stressors (Hughes & Stoney, 2000), whereas men experienced larger decreases in RSA to an emotion-induction task than women in another study (Yaroslavsky, Rottenberg, et al., 2013). However, many studies include either an all-female sample (Ahrens et al., 2008; Cyranowski et al., 2011; Nugent et al., 2011; Rottenberg et al., 2003; Yaroslavsky, Bylsma, et al., 2013; Yaroslavsky et al., 2014), all-male sample (Liang et al., 2015), or included sample sizes that were too small to reliably examine sex differences in these relationships. There were several studies that could have examined sex differences based on the equal inclusion of men and women or larger sample size, but these studies solely covaried for the potential effects of sex rather than examine it as a moderator (Bylsma et al., 2014; Licht et al, 2008; Yaroslavsky, Rottenberg, et al., 2013). Regardless of the paucity of this research, there have been several adult studies that have examined sex differences in HRV reactivity and symptoms of depression among samples of undergraduates or adults recruited from the community. In general, these studies have not found the presence of sex differences in these processes among adults (Gordon et al., 2012; Hughes & Stoney, 2000; Matthews et al., 2005).

Studies of children and adolescents more consistently have examined sex differences; however, the only adolescent study of clinical depression included

adolescent females only (Crowell et al., 2014), and a longitudinal study from late childhood into adolescence only included a sample of at-risk boys (Morgan et al., 2013). Several studies did not examine the potential moderating effects of sex on the relationship between HRV reactivity and depression (Pang & Beauchaine, 2013; Yaroslavsky et al., 2014). However, two studies of middle-aged children did examine sex differences, with one study demonstrating no differences between boys and girls in the relationship between RSA reactivity and depression (El-Sheikh et al., 2001) and one study finding that girls with increasing RSA and decreasing SNS response to the lab challenge reported greater depressive symptoms than boys with similar patterns (El-Sheikh et al., 2013). Overall, there remains a need for more systematic analyses of sex differences in adults and youth studies, particularly during the adolescent period and among those with current or remitted clinical depression. Future research also should examine potential sex differences in HRV reactivity to different stressor types, given research that women show greater physiological reactivity to social stressors than men, whereas men demonstrate greater reactivity to cognitive stressors (Stroud, Salovey, & Epel, 2002), particularly during adolescence (Rose & Rudolph, 2006; Stroud et al., 2009).

Curvilinear Models. Importantly, the findings of the present review indicate that in some studies *greater* HRV reactivity (specifically HF-HRV, RSA, or RMSSD) in the form of either PNS withdrawal (decreases) or PNS amplification (increases) is maladaptive, and *blunted* HRV reactivity or attenuated PNS withdrawal is indicative of depressed state or risk in other studies. Thus, a possible explanation for these seemingly contradictory findings may be that moderate HRV reactivity is best (Lovallo, Farag, Sorocco, Cohoon, & Vincent, 2012). For instance, it is possible that both hypo and hyper

reactivity may be maladaptive in most circumstances, with moderate HRV reactivity as the optimal response (Beauchaine, 2001; Porges, 2007). A recent study of cardiac vagal tone supports this notion (as indexed by resting RSA levels), finding that individuals with moderate resting RSA exhibited greater well-being, whereas those with both lower and higher resting RSA exhibited greater depressive symptoms (Kogan, Gruber, Shallcross, Ford, & Mauss, 2013). Although this study did not examine *reactivity* to a stressor, a similar pattern also may be present for RSA reactivity (and other indices of HRV) and depression, with both hyper or hypo responses indicative of greatest risk. In terms of the studies included in the present review, none of these studies examined quadratic patterns of HRV. Thus, it will be important for future research to replicate these findings of RSA levels with HRV reactivity and depression, which also may explain the variability of results across studies.

Environmental Context. Another important consideration to take into account in the examination between HRV reactivity and depression is environmental context. Several studies included in the present review found significant influences of environment (e.g., trauma history, conflict in the home, maternal depression) and HRV reactivity in depression (Cyranowski et al., 2011; El-Sheikh et al., 2013; Yaroslavsky et al., 2014). For instance, depressed women with a pronounced trauma history exhibited greater blunted reactivity to the lab stressor than non-depressed women or depressed women without a trauma history (Cryanowski et al., 2011). Similarly, although no known study has specifically evaluated childhood (or even adolescent) adversity or trauma and HRV reactivity in relation to clinical or subthreshold depression, a recent study by McLaughlin, Alves, and Sheridan (2014) found that childhood adversity predicted greater

internalizing symptoms among adolescents with reduced RSA reactivity during an anticipatory speech preparation phase. These findings are not surprising given research that trauma exposure impacts the limbic systems of the brain (e.g., for a review, see Tottenham & Sheridan, 2009), which are implicated in HRV reactivity and regulation (Thayer et al., 2012). This is also consistent with research on the HPA axis and cardiovascular reactivity, finding that adults with trauma histories demonstrate blunted reactivity to laboratory stressors (Carpenter et al., 2007; Lovallo et al., 2012; MacMillan et al., 2009). Beyond trauma, adversity in the form of other environmental influences, such as low socioeconomic status (Evans et al., 2013) and maternal depression (Blandon, Calkins, Keane, & O'Brien, 2008; Yaroslavsky et al., 2014), also may contribute risk for blunted HRV reactivity and potentially elevated depressive symptoms (Yaroslavsky et al., 2014). Thus, high-risk designs that examine potential risk factors for atypical HRV reactivity, and subsequently examine the development of depressive symptoms and disorders may provide useful information regarding the longitudinal role of HRV reactivity in depression. Further evaluation of potential moderating factors, including environmental influences, on the relationship between HRV reactivity and depression is needed, which may significantly impact patterns of HRV reactivity.

Transactional Model of HRV Reactivity to Stress, Stress Generation, and Depression

Although a review of the mechanisms underlying the relationship between HRV reactivity and depression is beyond the scope of the present study, it is important to briefly discuss potential pathways through which atypical or dysregulated HRV reactivity may be associated with depression and highlight these processes for future research. In understanding potential mechanisms, it would be most beneficial to understand the

temporal relationship between HRV reactivity and depression to determine whether HRV reactivity (and associated biopsychosocial processes) contributes to depression, or whether depression precedes and leads to atypical HRV reactivity. However, we propose that it could be both and that there could be a cyclical and transactional relationship between HRV reactivity and depression. For example, depression and/or biopsychosocial vulnerabilities to depression may lead to altered HRV reactivity, which subsequently contributes to the maintenance and recurrence of clinical depression. Alternatively, atypical HRV reactivity (potentially resulting from early environmental influences) may contribute to depression, which in turn, continues to alter and maintain dyregulated HRV reactivity. One potential mechanism that could explain this transactional relationship may be the influence of HRV reactivity as a contributor to the occurrence of stress. Specifically, we propose that individuals who display dysregulated HRV reactivity may directly or indirectly contribute to the occurrence of stressors in their lives. In this sense, individuals with atypical HRV reactivity may trigger stressors for which they are not physiologically, emotionally, or cognitively prepared or be able to adaptively respond, thereby heightening the risk of onset or maintenance of depression.

Consistent with this notion, individuals with current and remitted MDD consistently have been found to encounter higher levels of stressful events than their nondepressed counterparts, specifically events *dependent* on individuals' characteristics or behaviors (Daley et al., 1997; Hammen, 1991; Hammen & Brennan, 2002). This stress generation effect, whereby individuals shape their environments and contribute to the occurrence of stressors, has been prospectively documented among those with clinical, remitted, and subthreshold depression (Clements, Aber, & Seidman, 2008; Davila,

Hammen, Burge, Paley, & Daley, 1995; Hammen & Brennan, 2002; Hankin, Mermelstein, & Roesch, 2007; Liu & Alloy, 2010), and even among those with underlying vulnerabilities beyond the effects of depressive symptoms (Eberhart & Hammen, 2009; Hamilton, Stange, Kleiman, et al., 2013; Hamilton, Stange, Shapero, et al., 2013; McLaughlin & Nolen-Hoeksema, 2012). These stressors, in turn, predict depressive symptoms, as well as the onset, maintenance, and recurrence of clinical depression (Liu & Alloy, 2010).

Theories and research linking HRV reactivity to various neural regions, such as the amygdala and ventromedial prefrontal cortex, (Porges, 1997; Thayer & Lane, 2000; 2009; Thayer et al., 2012), indicate that HRV is associated with emotion intensity, regulation, and responding (Appelhans & Luecken, 2006; Fabes & Eisenberg, 1997; Thayer et al., 2012; Vasilev et al., 2009). Additionally, HRV is also linked with deficits in executive functioning and control, including attentional and memory processes (Hansen et al., 2003; Johnsen et al., 2003; Thayer & Brosscot, 2005), which have been associated with depression (Gotlib & Joorman, 2010). Attentional and emotion regulation are both crucial for adequate responding to stressful situations; thus, individuals who lack effective coping strategies may inadequately or inappropriately respond to stressors (Fabes & Eisenberg, 1997; Geisler et al., 2013), potentially eliciting subsequent stressors. In addition, dysregulated HRV reactivity has been found to be associated with neuroticism, considered to be a trait measure of stress and emotional reactivity (di Simplicio et al., 2011; Hughes, Howard, James, & Higgins, 2011; Jonassaint et al., 2009), which also prospectively predicts the occurrence of dependent stressors (Uliaszek et al., 2010). Further, HRV has been linked to maladaptive cognitive and emotional strategies,

such as cognitive reactivity, emotion suppression, and rumination (Yaroslavsky, Bylsma, et al., 2013). Although these personality, cognitive, and emotional vulnerabilities may not directly lead to stress, they may result in ineffective coping strategies for stress or behaviors that are poorly received by others and result in greater interpersonal stressors. In terms of potential behaviors, HRV also is associated with maladaptive behaviors (Porges, 2003b), including reduced interpersonal warmth (Diamond & Cribbet, 2013), poor social skills (Blair & Peters, 2003), social disengagement and withdrawal (Geisler, Kubiak, Siewert, & Weber, 2013), and impulsivity and hostility (Beauchaine, 2001; Crowell et al., 2014). These vulnerabilities and behaviors have been implicated in the stress generation process among adolescents and adults (Caldwell, Rudolph, Troop-Gordon, & Kim, 2004; McLaughlin & Nolen-Hoeksema, 2012; Molz et al., 2013; Uliaszek et al., 2010), which further exacerbates current depression or heightens the risk of future depression (for a review, see Liu, 2013).

Although these studies lend indirect support to HRV reactivity as a contributor to stress generation, a recent study indicated that lower RSA reactivity predicts more daily negative interactions among couples, thereby providing preliminary evidence for the relationship between RSA reactivity and heightened daily stressors (Diamond, Hicks, & Otter-Henderson, 2011). Consequently, it is possible that individuals with atypical HRV reactivity may trigger stressors through a variety of maladaptive responses and behaviors, which, in turn, contribute to a cascading effect of subsequent stressors, depression, and further dysregulated reactivity. Further, different patterns of reactivity, including blunted, exaggerated, and amplified reactivity, are associated with various aspects of these maladaptive behaviors and responses, which may help to explain some of the inconsistent

findings reviewed herein. Although this proposed model is novel and may potentially elucidate the relationship between HRV reactivity and depression, a direct empirical test of this model is needed. In particular, micro-longitudinal or daily study designs may be well-suited to explore the idiographic and complex relationships between HRV reactivity and depression, as well as the processes, such as the stress generation effect, potentially underlying this relationship.

Conclusions. Although this systematic review of the relationship between HRV reactivity and depression suggests that atypical HRV reactivity is implicated in depression, there are numerous questions remaining given the present state of research in the field. In short, future research is needed to better understand the individual differences in HRV reactivity and the contexts in which different atypical patterns may be associated with clinical, remitted, and subthreshold depression among youth and adults. Thus, prospective, multi-method, and longitudinal designs are needed to evaluate the relationship between HRV reactivity and depression across multiple developmental phases, and to examine potential mechanisms underlying this complex relationship. Once we can better identify the transactional processes through which physiological reactivity and depressive symptoms are associated, we can better identify those at risk and create prevention and intervention programs targeting these processes in at-risk individuals.

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APPENDIX A
SUPPLEMENTARY ANALYSES

Table 10. Sex Differences in Primary Study Variables

Measure	Women (N = 80)		Men (N = 25)		Statistical Difference
	M (N)	*SD (%)*	*M (N)*	*SD (%)*	*t* (X^2)
Demographic					
Race (White)	57	71	18	72	.01
Age	19.93	1.18	19.56	1.12	1.34
BMI	23.73	4.05	23.64	2.94	.11
MDD	62	78	16	64	1.82
RSA					
Baseline RSA	6.48	1.14	6.56	1.07	.31
Anticipatory RSA	6.38	1.15	6.53	1.07	.94
Stressor RSA	5.87	1.00	6.09	1.09	.54
Recovery RSA	6.34	1.14	6.28	1.07	.23
HR					
Baseline HR	75.11	10.44	76.53	8.83	.62
Anticipatory HR	81.32	11.88	82.69	9.18	.53
Stressor HR	91.73	14.80	91.20	11.19	.16
Recovery HR	75.26	10.76	76.19	9.04	.39
Daily Diary					
Int Dep Stress	1.56	.52	1.34	.48	1.77
Indep Stress	.39	.35	.26	.26	1.79
Dep Sx	10.89	2.90	11.12	3.73	.32

Note. * p <. 05; ** p < .01; *** p < .001. MDD = Major Depressive Disorder (Coded as 0 = None; 1 = Present); BMI = Body Mass Index; RSA = Respiratory Sinus Arrhythmia; HR = Heart Rate; Int Dep = Interpersonal Dependent; Indep = Independent; Dep Sx = Depressive Symptoms..

Table 11. Interactive Effects of RSA Predicting Depressive Symptoms

Variable	Depressive Symptoms		
	B	*SE*	*t*
Fixed Effects			
Intercept (Dep Sx)	9.74	2.32	4.20***
MDD	1.11	.56	1.97*
Sex (Female 0)	.58	.60	.96
Past Dep Med	.82	.61	1.34
BMI	.04	.07	.69
Cardio	2.42	1.45	1.55
T1 Dep Sx	.07	.01	6.24***
Resting RSA	-.55	.26	-.21*
RSA Rx	.31	1.08	.29
RSA x RSA Rx	-.01	.15	-.09
Random Effects			
Intercept (Dep Sx)	4.82	.82	5.91***

Note. * $p <$. 05; ** $p < .01$; *** $p < .001$. Dep Sx = Depressive Symptoms; MDD = Major Depressive Disorder (Coded as 0 = None; 1 = Present); Dep Med = Depressive Medication Use; BMI = Body Mass Index; Cardio = Heart condition; T1 = Time 1; RSA = Respiratory Sinus Arrhythmia; Rx = Reactivity.

Table 12. Interactive Effects of RSA Predicting Stressors

Variable	Interpersonal Dependent Stressors		
	B	*SE*	*t*
Fixed Effects			
Intercept (Int dep Stress)	.62	.45	1.38
MDD	.13	.11	1.15
Sex	.10	.13	.81
Past Dep Med	.02	.01	1.44
BMI	.02	.01	1.22
Cardio	.38	.29	1.29
T1 Neg Int Dep Stress	.05	.02	2.22*
Resting RSA	.08	.05	1.61
RSA Rx	-.17	.21	-.78
Resting RSA x RSA Rx	.01	.03	.17
Random Effects			
Intercept (Int dep Stress)	.18	.03	5.69***

Variable	Independent Stressors		
	B	*SE*	*t*
Fixed Effects			
Intercept (Indep Stress)	.45	.28	1.62
MDD	.04	.07	.53
Sex	.08	.08	1.11
Past Dep Med	-.06	.07	-.81
BMI	.03	.01	3.70***
Cardio	-.04	.17	-.24
T1 Indep Stress	.06	.02	3.42***
Resting RSA	-.01	.03	-.23
RSA Rx	.04	.13	.31
Resting RSA x RSA Rx	-.01	.02	-.74
Random Effects			
Intercept (Indep Stress)	.06	.01	4.82

Note. * p <. 05; ** p < .01; *** p < .001. Int dep = Interpersonal dependent; MDD = Major Depressive Disorder (Coded as 0 = None; 1 = Present); Dep Med = Depressive Medication Use; BMI = Body Mass Index; Cardio = Heart condition; T1 = Time 1; Neg = Negative; RSA = Respiratory Sinus Arrhythmia; Rx = Reactivity; Indep = Independent

Table 13. Interactions of RSA Reactivity and Sex predicting Depressive Symptoms

Variable	Depressive Symptoms		
	B	*SE*	*t*
Fixed Effects			
Intercept (Dep Sx)	9.67	2.34	4.14***
MDD	1.11	.56	1.97*
Sex (Female 0)	-.49	.70	-.71
Dep Med	.84	.62	1.37
BMI	.04	.07	.65
Cardio	2.26	1.45	1.56
T1 Dep Sx	.07	.01	6.24***
Resting RSA	-.54	.36	-2.09*
RSA Rx	.38	.68	.55
RSA Rx x Sex	-.18	.72	-.25
Random Effects			
Intercept (Dep Sx)	4.82	.82	5.91***

Note. * p <. 05; ** p < .01; *** p < .001. Dep Sx = Depressive Symptoms; MDD = Major Depressive Disorder (Coded as 0 = None; 1 = Present); Dep Med = Depressive Medication Use; BMI = Body Mass Index; Cardio = Heart condition; T1 = Time 1; RSA = Respiratory Sinus Arrhythmia; Rx = Reactivity.

Table 14. Interactions of RSA Patterns and Sex Predicting Stress Generation

Variable	Interpersonal Dependent Stressors		
	B	*SE*	*t*
Fixed Effects			
Intercept (Int dep Stress)	.39	.47	.84
MDD	.12	.11	1.12
Sex	.65	.70	.92
Dep Med	.17	.12	1.47
BMI	.02	.01	1.24
Cardio	.36	.29	1.23
T1 Neg Int Dep Stress	.05	.02	2.22*
RSA Rx	-.12	.06	-2.16*
Resting RSA	.06	.06	1.07
Resting RSA x Sex	.08	.11	.79
Random Effects			
Intercept (Int dep Stress)	.18	.03	5.69***

Variable	Interpersonal Dependent Stressors		
	B	*SE*	*t*
Fixed Effects			
Intercept (Int dep Stress)	.53	.44	1.20
MDD	.12	.11	1.10
Sex (Female 0)	-.19	.14	1.38
Dep Med	.19	.12	1.62
BMI	.02	.01	1.16
Cardio	.38	.29	1.31
T1 Neg Int Dep Stress	.05	.02	2.35*
Resting RSA	.09	.05	1.71
RSA Rx	-.16	.06	-2.66**
RSA Rx x Sex	.19	.14	1.35
Random Effects			
Intercept (Int dep Stress)	.18	.03	5.68***

Note. * $p <$. 05; ** $p < .01$; *** $p < .001$. Int dep = Interpersonal dependent; MDD = Major Depressive Disorder (Coded as 0 = None; 1 = Present); Dep Med = Depressive Medication Use; BMI = Body Mass Index; Cardio = Heart condition; T1 = Time 1; Neg = Negative; RSA = Respiratory Sinus Arrhythmia; Rx = Reactivity.

APPENDIX B

PHYSIOLOGICAL MARKERS OF AFFECT REACTIVITY

Daily diary studies of affective reactivity suggest that individuals with current Major Depressive Disorder (MDD) demonstrate greater increases in negative affect to daily stressors compared to healthy controls (Bylsma, Taylor-Clift, & Rottenberg, 2011; Myin-Germeys et al., 2003; O'Hara, Armeli, Boynton, & Tennen, 2014). Importantly, greater negative affective reactivity to daily stressors also has been found among individuals with subthreshold depression (Bylsma et al., 2011) and undergraduates with a history of depression (O'Hara et al., 2014). Relatedly, increases in negative affect to daily stressors predict subsequent increases in depressive symptoms (Cohen et al., 2005).

Although ANS activity has been examined with concurrent trait and lab-induced state levels of negative affect (Cribbet, Williams, Gunn, & Rau, 2011), surprisingly fewer studies have examined physiological processes in relation to affective reactivity to naturally-occurring stressors (Fabes & Eisenberg, 1997). However, lower resting RSA (which is associated with blunted RSA reactivity (Yaroslavsky, Rottenberg, et al., 2013)) predicted more negative emotional arousal following daily stressors (Fabes & Eisenberg, 1997). These findings highlight the importance of examining patterns of reactivity across multiple domains and risk factors for depression, and of determining whether physiological reactivity to laboratory-induced stress maps onto daily affective reactivity to naturally-occurring daily stressors.

Thus, another primary aim was to examine whether physiological reactivity contributed to affective reactivity to naturally-occurring stressors. A further secondary

aim was to examine whether affective reactivity would mediate the relationship between blunted RSA reactivity and depressive symptoms. Given research providing preliminary support for these relationships (Diamond et al., 2011; Fabes & Eisenberg, 1997), we hypothesized that blunted RSA reactivity would predict greater affective reactivity to daily stressors. Further, we also expected that affective reactivity would mediate the relationship between blunted RSA reactivity and depressive symptoms.

Method (Additional)

Daily Affective Reactivity to Stressors. Negative Affective (NA) reactivity to daily stressors was assessed using items from the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988). Following each stressor, participants completed three items to assess affective response. Participants used a 5-point scale (1 = very slightly or not at all, 5 = extremely) to rate the extent to which they felt sad, irritable, and nervous following each event. The scores were added for all stressful events endorsed, and then divided by the total number of events endorsed (for an average level of emotional reactivity to stressors, given that a total sum would result in greater scores for those who endorsed more stressors). In addition, we also separately examined each type of affect (average levels of sadness, irritability, nervousness) to determine specificity of affective reactivity. The NA scale of the PANAS is a reliable and valid measure of state affect (Bylsma et al., 2011; Cohen et al., 2005; Watson, 1988), and the internal reliability of the NA and PA subscale in the present study was .91 and .80, respectively.

Hypothesis Testing Analyses

To determine whether physiological reactivity predicted affective reactivity to stressors, multilevel modeling (MLM) using Mplus 7.0 (Muthen & Muthen, 2007) was used to test hypotheses. Thus, data from the 14 daily assessments (e.g., affect) were Level 1 variables and data from the Time 1 assessment (e.g., RSA reactivity) were Level 2 variables. MLM is also advantageous because it uses Maximum Likelihood to estimate parameters for individuals with missing data (e.g., missing one daily diary assessment), which maximizes data use and prevents unnecessary exclusion of participants from analyses.

To test our primary aim that blunted RSA reactivity would predict greater affective reactivity to stressors, we entered RSA reactivity as a Level 2 variable predicting the intercept of daily affective reactivity (Level 1 variable). For our mediational hypothesis that daily affective reactivity would mediate the relationship between physiological reactivity and depressive symptoms, we entered RSA reactivity as the main Level 2 predictor variable for these analyses and daily depressive symptoms served as the dependent variable in these analyses, controlling for previous day depressive symptoms. To better understand the relationship of each mediating piece, we evaluated each mediation leg prior to testing the indirect effect (e.g., daily affective reactivity to depressive symptoms). Further, mediation analyses were conducted even when there was no direct relationship between the independent and dependent variables given research indicating that an indirect effect is possible even when there is no direct effect (Preacher, 2007).

Results

In terms of our hypothesis for affective reactivity to daily stressors, we found that there was no main effect of RSA reactivity on affective reactivity (Table 15). For our mediation analyses, we found that affective reactivity significantly predicted daily depressive symptoms (t = 8.40, p < .001), controlling for prior day levels of depressive symptoms. Further, we did not find evidence for an indirect effect between RSA reactivity to depressive symptoms via affective reactivity to stressors (B = 9.34, SE= 4.08, t = 2.29, p = .02).

Table 15. RSA Reactivity Predicting Affective Reactivity to Stressors

Variable	Affective Reactivity		
	B	*SE*	*t*
Fixed Effects			
Intercept (Affect Rx)	**1.25**	**1.25**	**1.97***
MDD	.30	.44	.91
Sex	.30	.49	.62
Past Dep Med	-.04	.44	-.09
BMI	.04	.05	.82
Cardio	.20	1.12	.18
Resting RSA	.31	.20	1.56
RSA Rx	-.11	.22	-.52
Random Effects			
Intercept (Affect Rx)	2.19	.45	4.91***

Note. * p <. 05; ** p < .01; *** p < .001. MDD = Major Depressive Disorder (Coded as 0 = None; 1 = Present); Dep Med = Depressive Medication Use; BMI = Body Mass Index; Cardio = Heart condition; RSA = Respiratory Sinus Arrhythmia; Rx = Reactivity.