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

Jessica L. Hamilton¹ and Lauren B. Alloy¹

Temple University, Department of Psychology, 1701 N. 13th St., Philadelphia, PA 19122, United States

Abstract

Heart rate variability has received growing attention in the depression literature, with several recent meta-analyses indicating that lower resting heart rate variability is associated with depression. However, the role of fluctuations in heart rate variability (or reactivity) in response to stress in depression remains less clear. The present review provides a systematic examination of the literature on heart rate variability *reactivity* to a laboratory-induced stressor task and depression, including 26 studies of reactivity in heart rate variability and clinical depression, remitted (or history of) depression, and subthreshold depression (or symptom-level depression) among adults, adolescents, and children. In addition to reviewing the findings of these studies, methodological considerations and conceptual gaps in the literature are addressed. We conclude by highlighting the importance of investigating the potential transactional relationship between heart rate variability reactivity and depression and possible mechanisms underlying this relationship.

Keywords

heart rate variability; depression; stress; reactivity; respiratory sinus arrhythmia

1. Introduction

Cardiovascular disease and depression are two of the world's leading causes of mortality and disability (Murray & Lopez, 1997), with recent research documenting the considerable link between these two debilitating conditions (e.g., Grippo & Johnson, 2009; Van der Kooy et al., 2007). Indeed, meta-analyses indicate that depression increases the risk for coronary heart disease among adults (Rugulies, 2002; Wulsin & Singal, 2003) and adolescents (Bylsma et al., 2015), and may be a more important risk factor for cardiovascular disease than smoking or diabetes (Van der Kooy et al., 2007). Specifically, abnormalities in the

Correspondence concerning this article should be addressed to Jessica L. Hamilton, Department of Psychology, Temple University, Weiss Hall, 1701 N. 13th Street, Philadelphia, PA 19122. (Phone: 516-399-0268; Jessica.leigh.hamilton@temple.edu).

¹Temple University

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autonomic nervous system (ANS) related to cardiac activity, especially in response to stress, have been identified as potential mechanisms linking depression and poor cardiovascular health (Grippe & Johnson, 2009). Given this relationship, delineating the role of autonomic cardiac reactivity in depression may provide important information for the treatment and prevention of two serious physical and mental health conditions. Thus, this article begins with an overview of the ANS and a physiological marker of the ANS, heart rate variability (HRV), before reviewing the current state of the literature on HRV reactivity and depression.

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

Theory and research implicate the brain's influence on the heart in the extent to which individuals can successfully respond and adapt to environmental challenges and self-regulate (Porges, 1995, 2007; Thayer & Lane, 2000). 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, the heart's primary "pace maker" (Appelhans & Luecken, 2008; Berntson et al., 1997). In particular, the parasympathetic nervous system (PNS) influence on the heart through the vagus nerve (the tenth cranial artery) has received much attention (Porges, 1995, 2007). According to the Polyvagal theory (Porges, 1995), vagal control of the heart, commonly referred to as cardiac vagal control, promotes a decrease in heart rate and functions as a vagal "brake" (Porges, 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 stress typically elicits vagal withdrawal and release of the brake, decreasing control of the heart via the vagus nerve. Release of the vagal "brake" facilitates the activation of the sympathetic nervous system (SNS) when confronted with stress to mobilize physiological and cognitive resources to effectively cope and respond. However, augmentation of the vagal brake slows heart rate and inhibits activation of the SNS. Thus, greater vagal withdrawal reflects *greater reactivity* of the PNS and is generally considered to be an adaptive response to stress (Porges, 1995). Although *exaggerated* reactivity of the ANS is associated with negative health outcomes (Chida, Hamer, & Steptoe, 2008), ANS reactivity (to a point) is reflective of an adaptive stress response.

In terms of cardiac function, the heart is dually innervated by both the SNS and PNS. SNS 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, PNS 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 SNS 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 two 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 or react to environmental challenges (*reactivity*; Porges, 1995; 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, Ahs, Fredrikson, Sollers, & Wager, 2012).

Although the specific methods and measures of HRV are beyond the scope of the present review and are reviewed elsewhere (Xhyheri, Manfrini, Mazzolini, Pizzi, & Bugiardi, 2012), a brief synopsis of these calculations is pertinent to understanding the present review. In brief, there are two main methods used to quantify HRV levels and fluctuations, including time-based and frequency-based (or spectral analysis) approaches. 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), which can be quantified using an electrocardiogram (ECG). Frequency-based measures of HRV compute the SNS influences through Low Frequency HRV (LF-HRV; .04-.15 hertz), PNS influences through High-Frequency HRV (HF; .15-.40 hertz), and the SNS-PNS dynamic through the ratio of low to high frequencies (LF/HF ratio). It is important to note that HF-HRV is highly related to respiratory sinus arrhythmia (RSA), which is HRV that occurs over the respiratory cycle (often at higher frequencies), as well as the time-based root mean square successive differences (RMSSD) (Beauchaine, 2001; Xhyheri et al., 2012). Although these indices may not completely estimate vagal withdrawal, they are considered to be non-invasive measures of ANS activity that reflect more central regulatory processes in the brain (Grossman & Taylor, 2007).

1.2 Heart Rate Variability in the Context of Depression

In recent years, indices of HRV (particularly HF-HRV and RSA) have received considerable attention in the depression literature. Although resting levels and reactivity of HRV may be correlated with one another (Porges et al., 1996; Salomon, 2005), these indices reflect different regulatory processes. Specifically, whereas resting levels may reflect the *capacity* to respond and autonomic flexibility, HRV reactivity reflects acute changes in self-regulation and state mood in the physiological response compared to rest (Beauchaine, 2001; Porges, 1995). In particular, HRV not only reflects physiological regulation, but also cognitive and emotional regulation (Appelhans & Luecken, 2006; Porges, Doussard-Roosevelt, Portales, & Greenspan, 1996; 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 executive functioning (Appelhans & Luecken, 2006; Thayer & Brosschot, 2005). Further, greater capacity to respond to environmental challenges (i.e., greater RSA reactivity) 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 resting HRV have been found to have poorer emotion regulation abilities and deficits in attentional control and working memory (Appelhans & Luecken, 2006; Thayer & Brosschot, 2005).

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

(Gotlib & Joormann, 2010), HRV has garnered interest in depression. There are two comprehensive reviews or meta-analyses of the relationship between HRV and depression (Kemp et al., 2010; Rottenberg, 2007). Evaluating RSA and depression among clinically depressed adults, Rottenberg (2007) found a modest association between RSA levels and depression ($d = 0.33$, $CI = .18-.49$), such that depressed individuals demonstrated significantly lower resting RSA compared to non-depressed or healthy controls. However, Rottenberg (2007) only reviewed cross-sectional studies, which limited the ability to draw conclusions regarding the temporal relationships between RSA and depression. In addition, participants' RSA levels in response to antidepressant medication over the course of depression were included in several studies. Finally, and most pertinent to the purpose of the present review, Rottenberg did not evaluate the associations between RSA *reactivity* in response to a psychological challenge and depression.

To address these gaps, Kemp and colleagues (2010) conducted a meta-analysis of the impact of HRV on depression and included studies that evaluated several HRV indices (including time domain, HF, LF, LF/HF ratio). Included studies also were required to have unmedicated individuals with Major Depressive Disorder (MDD) and either 1) an age-matched control group without MDD, 2) reported measures of depression severity among the MDD group, or 3) pre-and post-treatment comparisons of an MDD group. Overall, meta-analysis revealed that depression was associated with lower HF-HRV (RSA) levels and increases in LF/HF ratio (i.e., lower 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 HF-HRV than those with less severe depression. Similar to Rottenberg's (2007) meta-analysis, 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 extended Rottenberg's (2007) findings, this review 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 whether HRV is a marker of current depression or vulnerability for depression. Despite these limitations, these reviews demonstrate 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.

1.3 Developmental Influences on HRV Reactivity and Depression

Another major limitation of the reviews discussed above is the focus on adult samples and absence of studies examining HRV and depression among children and adolescents. Examining markers of depression risk in youth is important for many 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 among younger individuals may provide useful information regarding the temporal relationships between these processes. Indeed, a recent meta-analytic review by Koenig, Kemp, Beauchaine, Thayer, and Kaess (2016) evaluated resting levels of HF-HRV in relation to

clinical depression and depressive symptom severity in youth. This review indicated that lower resting levels of HF-HRV were found in clinically depressed adolescents, but there was no significant effect of HF-HRV on depressive symptoms in community samples. However, simultaneously reviewing studies of both adults and youth may provide valuable information regarding changes in HRV reactivity to stressors across development, as well as potential differences in the effects of HRV reactivity on depression during distinct developmental stages. For instance, research indicates that there are developmental changes in both resting RSA and RSA reactivity across the lifespan, such that RSA reactivity to challenges increases during the early stages of life (e.g., Bar-Haim, Marshall, & Fox, 2000; Wilkinson & Howse, 2003), stabilizes during middle to later childhood and adolescence (El-Sheikh, 2005; Hinnant, Elmore-Staton, & El-Sheikh, 2011), and declines from adolescence to adulthood (Hollenstein, McNeely, Eastabrook, Mackey, & Flynn, 2012). Importantly, several studies also indicate that there is variability in whether some individuals experience increases or decreases in RSA reactivity to stressors (Hinnant et al., 2011; Pang & Beauchaine, 2013), suggesting that there may be substantial environmental influences in the development of atypical reactivity, particularly among individuals at risk for depression (Gentzler, Rottenberg, Kovacs, George, & Morey, 2012). In particular, youth at risk for depression, such as children of depressed mothers, do not demonstrate developmental increases in RSA (Field & Diego, 2008; Gentzler et al., 2012), suggesting that high-risk youth may be at greater risk for atypical reactivity. Further, there are a number of changes that occur during adolescence that may influence the development of atypical HRV reactivity, including pubertal and biological influences (Casey, Jones, & Hare, 2008; Susman & Rogol, 2004), and greater exposure and reactivity to stress (Hamilton, Stange, Abramson, & Alloy, 2015; Romeo, 2013). Thus, adolescence may be a period in which individuals with atypical HRV reactivity are at increased risk for depression, thereby further highlighting the need for a thorough review of HRV reactivity and depression among both youth and adults.

1.4 The Present Review

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. The present review examines HRV reactivity to stressor tasks in relation to both current and past depressive disorders and depressive symptoms. Further, given developmental differences in HRV reactivity among children, adolescents, and adults, we review studies of HRV reactivity and depression in samples of both adults and youth.

2. Method

There is an impressive amount of research that has examined the role of HRV in psychopathology, as well as various medical conditions. In particular, considerable research evaluates resting HRV and reactivity of HRV in psychological disorders that are highly

comorbid with depression, including 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), although there is a need also to expand this literature to HRV reactivity. There also has been a recent review of 134 studies spanning over 50 years on emotion in relation to ANS reactivity, including HRV variables (Kreibig, 2010). Thus, although there is a plethora of research that could be included through its connection to depression, our review focuses solely on studies that included HRV reactivity and 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.

3. Results

3.1 Included Studies

The search within the electronic databases PsycINFO and MEDLINE for HRV reactivity in depression revealed a total of 273 studies as of January 2016 and an additional 12 studies were identified for review from study abstracts. The total number of studies was reduced to 26 after determining whether the study met inclusion and exclusion criteria by examining the study abstracts or full 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 (e.g., brooding), evaluated HRV reactivity in response to a non-psychological stressor (e.g., postural changes), or included treatment effects on HRV reactivity (e.g., psychopharmacological treatment). Of those studies that met inclusion and exclusion criteria, 19 (73%) were studies of adult samples (over age 18), six (23%) examined HRV reactivity in children or adolescents, and one (4%) examined RSA reactivity in both adults

and children (offspring). Thus, the following sections are divided based on studies that included adults versus samples of children and adolescents.

3.2 Types of Stressor 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 (see Table 1 for more information). Overall, of the 20 adult studies, 9 (45%) studies included a cognitive task, 6 (30%) included a social stressor, and 10 (50%) included an emotion-induction task. Several adult studies ($N = 5$; 25%) included multiple stressor conditions and most allowed for a recovery period between tasks. In addition, the seven youth studies only included social ($N = 4$; 57%) and emotion-induction tasks ($N = 3$; 43%), but no cognitive stressor tasks were utilized. All studies included a baseline period to allow for habituation and a measure of baseline HRV, which served as the comparison or covariate for measuring 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 reading (Bylsma et al., 2014; Gordon, Ditto, & D'Antono, 2012).

3.2.1 Cognitive Stressors—The cognitive tasks consisted of numerical tasks, including random number generation (Shinba, 2014; Shinba et al., 2008), a calculation task in which the participants count aloud backwards 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 decide the parity of numbers (Silvia, Nusbaum, Eddington, Beaty, & Kwapil, 2014). Other cognitive tasks included a mirror star tracing task (MSST), in which participants trace a star quickly and accurately while only seeing the mirror image of the star and receiving loud noise feedback when the stylus is not in contact with the star (Matthews, Nelesen, & Dimsdale, 2005; Rottenberg, Clift, Bolden, & Salomon, 2007). Two studies also utilized computer tasks, such as a concentration task (Ahrens et al., 2008) and N-Back task with increasing levels of difficulty (Nugent, Bain, Thayer, Sollers, & Drevets, 2011).

3.2.2 Socio-Evaluative Stressors—Social stressors generally included variations of a speaking task with social evaluative threat. The most commonly used situation was one in which participants defended themselves from an offense, such as being wrongly accused of theft or defending themselves against a traffic ticket (Ahrens et al., 2008; Bylsma et al., 2014; Cyranowski, Hofkens, Swartz, Salomon, & Gianaros, 2011; Hughes & Stoney, 2000; Panaite et al., 2016; Rottenberg et al., 2007). Another study included role-playing tasks, such as providing negative feedback to an employee and an unscripted debate on abortion (Gordon et al., 2012). Among children, most social stressors included listening to an audiotape of a negative interaction between a man and women, such as a disagreement (El-Sheikh, Harger, & Whitson, 2001; El-Sheikh et al., 2013). Other stressors included a “hot topics” discussion with a parent on an interpersonal conflict (Crowell et al., 2014) or a topic mutually rated as stressful by the parent and adolescent, such as household chores (Morgan, Shaw, & Forbes, 2013).

3.2.3 Emotion-Induction Stressors—Emotion-induction films were included as they are considered to be a form of psychological stress. Most film clips were a sadness-induction (Rottenberg, Wilhelm, Gross, & Gotlib, 2003), usually a clip from “The Champ” in which a boy is grieving over the death of his father (Panaite et al., 2016; Pang & Beauchaine, 2013; Rottenberg, Salomon, Gross, & Gotlib, 2005; Yaroslavsky, Bylsma, Rottenberg, & Kovacs, 2013a; Yaroslavsky, Rottenberg, & Kovacs, 2013b; Yaroslavsky, Rottenberg, & Kovacs, 2014). For children, sadness-inducing film clips included the scene from “The Lion King” when the young lion is 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 used scripted emotional narratives categorized as pleasant, unpleasant, and neutral (Benvenuti, Mennella, Buodo, & Palomba, 2015), and one involved recall of anger experiences—though this was not separately analyzed from the cognitive stressor (Ehrenthal et al., 2010).

3.3 Calculation of HRV Reactivity

There also was heterogeneity in the calculation of HRV reactivity across studies. The majority (15) of studies calculated reactivity by subtracting mean levels during the stressor task from the resting or baseline levels, whereas other studies utilized a residualized change score by regressing the average levels from the baseline period to the stressor task phase. Both methods take into account the initial and task levels of fluctuations of HRV or reactivity (in various directions). Another method utilized ratio scores of HRV for the stressor versus rest, with greater scores indicating greater reactivity during the challenge (Shinba et al., 2008; 2014).

3.4 Adult studies of HRV reactivity to a psychological stressor and depression

3.4.1 Current Depression—Of the 20 studies examining HRV reactivity in depression among adults, 11 included a sample of adults with current MDD (Table 1). These studies predominantly examined RSA or HF-HRV reactivity in individuals diagnosed with MDD versus a control group of healthy individuals (Bylsma et al., 2014; Cyranowski et al., 2011; Ehrenthal et al., 2010; Rottenberg et al., 2003; 2007; Yaroslavsky et al., 2014), and two studies examined RSA reactivity in the course of depression among those with MDD (Panaite et al., 2016; Rottenberg et al., 2005). Three studies also included the other indices of HRV, including LF-HRV and LF/HF ratio, in MDD versus control groups (Liang et al., 2015; Nugent et al., 2011; Shinba et al., 2014). Overall, the majority of the studies ($N = 9$; 82%) found that currently depressed individuals demonstrated *atypical* RSA reactivity to the stressor conditions, whereas their non-depressed counterparts experienced the expected RSA decrease (or withdrawal/reactivity) during the stressor task (Bylsma et al., 2014; Cyranowski et al., 2011; Ehrenthal et al., 2010; Liang et al., 2015; Rottenberg et al., 2003; 2007; Shinba et al., 2014). This *atypical* HRV reactivity seems to be 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.

Specifically, Bylsma and colleagues (2014) found that MDD individuals exhibited blunted RSA reactivity to a speech stressor in which participants defended themselves from a traffic ticket. Other studies similarly demonstrated that the MDD group had blunted reactivity to cognitive and emotion-induction stressors (Cyranowski et al., 2011; Ehrental et al., 2010; Liang et al., 2015; Rottenberg et al., 2003; 2007; Shinba et al., 2014) compared to controls, suggesting that those with MDD may exhibit blunted reactivity to multiple types of stressors. For instance, Ehrental and colleagues utilized a combined stress task of mental arithmetic and anger-recall among 25 inpatients with a depression diagnosis and 25 healthy individuals, also finding reduced HF-HRV reactivity among those with MDD. Interestingly, Rottenberg and colleagues (2007) found that healthy individuals demonstrated RSA decreases during the speech and cognitive stressors (mirror-tracing tasks), but the MDD group did not. Individuals with MDD actually experienced *increases* in RSA (or RSA amplification) during the stressors, thereby highlighting the complexity of RSA reactivity. Liang and colleagues (2015) also found a non-significant trend for men with MDD to have increases in HF-HRV to the cognitive stressor compared to controls, noting that there were distinct RSA reactivity patterns between those with and without MDD. Further, Cyranowski and colleagues (2011) found evidence that depressed women demonstrated lower RSA during an emotion-induction of affection (love/infatuation), whereas healthy women experienced the expected increase. However, depressed women with a trauma history exhibited blunted RSA levels during the speech stressor compared with both nondepressed women and depressed women with little or no trauma history, suggesting that prior exposure to environmental stressors may influence atypical HRV reactivity and its relationship to depression. To date, only two studies did not find differences between the depressed and nondepressed groups during the mental stressor of the n-back task (Nugent et al., 2011) or a sad film clip (Yaroslavsky et al., 2014), but there was evidence of blunted reactivity in HF-HRV and LF/HF ratio during the non-mental stressor of a motor task (Nugent et al., 2011).

Only two studies longitudinally examined HRV reactivity in depressed adults (Panaite et al., 2016; Rottenberg et al., 2005). These studies found that individuals with greater RSA reactivity (or withdrawal) to a sad film, but not an anger or amusement/happy film, were more likely to have overall depressive symptom improvement or remission six-months later, whereas those with *blunted* RSA reactivity were more likely to still be depressed or have a poorer depression trajectory. Blunted RSA reactivity to a speech stressor also predicted maintenance and speed of depression symptom improvement six months later (Panaite et al., 2016). These studies highlight the importance of RSA reactivity in predicting longitudinal outcomes among depressed individuals. Of note, these were the only studies to examine HRV reactivity in current depression over a follow-up period and not just the correlation between HRV reactivity and depression at one study visit (as in the previously discussed studies).

Although most studies have solely evaluated RSA or HF-HRV, three studies also examined the reactivity of LF/HF ratio and LF effects in depression with mixed findings. Shinba and colleagues (2014) obtained evidence for blunted reactivity for the LF/HR ratio among depressed individuals compared to nondepressed controls in response to a cognitive stressor, the random number generation task. However, 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- the N-back task, which was similar to their findings for HF-HRV. There were no significant differences between groups in LF-HRV reactivity. However, the results from 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 men 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 enhanced nor attenuated reactivity to the stressor, but rather a different trend of HRV reactivity to stress between depressed and nondepressed groups.

3.4.2 Remitted Depression—In total, six studies examined HRV reactivity in adults with remitted depression compared to healthy controls with primarily null findings (Table 2). Most 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, et al., 2013a; Yaroslavsky et al., 2013b; Yaroslavsky et al., 2014). For instance, Ahrens and colleagues (2008) compared 22 women with remitted depression and 20 healthy controls on three stressor tasks, including a speech, mental arithmetic, and cognitive computer task, but found no significant differences between groups on HF-HRV reactivity. This study is the only one to examine other indices of HRV, and did not find significant differences between those with and without a history of depression on LF or LF/HF ratio of HRV reactivity (Ahrens et al., 2008).

However, 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 depressive symptoms in the context of higher resting RSA, and low resting RSA and RSA withdrawal (atypical RSA pattern) predicted remitted depression status (Yaroslavsky et al., 2013b; Yaroslavsky et al., 2014). Further, Yaroslavsky and colleagues (2013a) also found that women with greater RSA reactivity (decreases in RSA) and high resting RSA were less likely to report maladaptive 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.

Importantly, two studies also have evaluated whether HRV reactivity is a state-dependent marker of depression by comparing two groups: individuals with remitted MDD versus individuals with current MDD (Bylsma et al., 2014; Yaroslavsky et al., 2014; Table 1). These studies yielded inconsistent findings, with Yaroslavsky and colleagues (2014) failing to find evidence that RSA reactivity significantly differed among those with current versus remitted depression. RSA reactivity in combination with resting RSA also did not

significantly differentiate current and remitted depressed groups. Both current and remitted MDD groups demonstrated atypical RSA patterns (described previously), which were significantly different than controls. However, Bylsma and colleagues (2014) found that only individuals with current MDD, and not those with a history of MDD, demonstrated blunted RSA reactivity to a speech stressor task compared to the control group. These studies suggest that more research comparing current and remitted MDD is needed to determine whether HRV reactivity is dependent on mood or mood state-independent.

3.4.3 Depressive symptoms—Eight studies have moved beyond clinical depression to evaluate whether HRV reactivity is associated with elevated depressive symptoms (Benvenuti et al., 2015; Gordon et al., 2012; Hughes & Stoney, 2000; Matthews et al., 2008; Shinba, 2008; Silvia et al., 2014; Yaroslavsky et al., 2013a; 2013b; Table 3), which has the potential to indicate whether HRV reactivity is not a *scar* resulting from a depressed episode or dependent on depressed state, but a marker of depression risk. Similar to the aforementioned studies with remitted and current depression, the findings are mixed. For instance, three studies (37.5%) found significant effects of HF-HRV/RSA reactivity on depressive symptoms, but in different directions. For instance, 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 reactivity is associated with elevated depressive symptoms. Consistent with the findings on current MDD, however, two studies demonstrated that reduced HF-HRV reactivity was associated with elevated depressive symptoms (Benvenuti et al., 2015; Shinba et al., 2008). Interestingly, Benvenuti and colleagues (2015) found that individuals with dysphoria (elevated depressive symptoms) experienced reduced RSA/RMSSD reactivity to a pleasant, but not unpleasant or neutral, emotion induction compared to individuals without dysphoria. This study indicates that dysphoric individuals may not only have reduced HRV reactivity to negative emotional stressors, but also less physiological reactivity to positive environmental contexts. However, more research is needed to replicate these findings, particularly given the null results with the amusing/happy inductions among currently depressed adults (Ehrenthal et al., 2010; Panaite et al., 2016; Rottenberg et al., 2005).

In contrast, five studies (62.5%) failed to find evidence of the main effects of HRV reactivity, including HF-HRV, LF-HRV, and RSA, on heightened depressive symptoms on either cognitive (Matthews et al., 2005; Silvia et al., 2014), socio-evaluative (Gordon et al., 2012), or emotion tasks (Yaroslavsky et al., 2013a; 2013b). For instance, in one study, 199 healthy men and women (unmedicated with no psychiatric history), participated in a social stressor task in which participants had to role play hostile behavior towards a confederate and participate in a debate on abortion (Gordon et al., 2012). However, HRV reactivity (HF, LF, or LF/HF ratio) was not associated with elevated depressive symptoms (defined as having a score of 13 or more on the Beck Depression Inventory; Gordon et al., 2012). Similarly, Matthews and colleagues (2005) did not find significant differences in HF-HRV reactivity to a cognitive stressor (Mirror Star Tracing Task) by depressive symptom levels among 91 adults with no psychiatric history. Further, Silvia and colleagues (2014) also did not find that depressive symptoms predicted RSA reactivity to a cognitive stressor (i.e. parity task) among 131 undergraduate students; however, this study also found no significant changes in

RSA from baseline to stressor, suggesting that this task did not sufficiently induce RSA changes in the sample. Finally, two studies (Yaroslavsky et al., 2013a; 2013b) utilized the same sample of individuals with juvenile history of depression (Yaroslavsky, Bylsma, et al., 2013a included only the female participants), and found no main effects of RSA reactivity on depressive symptoms. However, similar to their other findings, atypical patterns of resting RSA and RSA reactivity predicted greater increases in depressive symptoms to the sad film, controlling for prior depression history.

Given the paucity of research and the 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 sets of criteria (e.g., diagnostic criteria) as the basis of study inclusion, the samples included in the studies investigating depressive symptoms were heterogeneous in depression measures and samples, including undergraduate samples (Hughes & Stoney, 2000; Matthews et al., 2005; Silvia et al., 2014), a community sample of adults across ages 18-65 (Gordon et al., 2012), individuals in a business company (Shinba et al., 2014), and individuals with remitted depression and healthy controls collapsed across studies for symptom analyses (Yaroslavsky, Rottenberg, et al., 2013). Further, three studies specifically excluded anyone with current or past psychiatric disorders (Gordon et al., 2012; Matthews et al., 2005; Shinba et al., 2008), whereas two did not screen out individuals with other psychiatric disorders (Hughes & Stoney, 2000; Silvia et al., 2014). Given the variability of samples included (such as those with prior depression histories; Yaroslavsky et al., 2013a; 2013b), conclusions about HRV reactivity in subthreshold depression are unclear and we are unable to determine whether HRV reactivity is a marker of future risk. Importantly, none of these symptom-level studies with adults have evaluated the prospective prediction of depressive symptoms, which will be important in differentiating whether HRV reactivity is a consequence or correlate of depression or a marker of vulnerability to future depression.

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

To date, only seven studies have evaluated HRV reactivity in depression among children and adolescents (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 4). Although there are additional studies that have examined internalizing symptoms, it is important to differentiate these studies to better parse out effects specific to depressive symptoms. Of note, however, Graziano and Derefinko (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 studies 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). Of the seven total studies of youth, two compared youth with and without depressive disorders, three examined RSA reactivity among high-risk youth, and two examined RSA reactivity among community samples of children in relation

to depressive symptoms. These studies are reviewed separately. Across studies, only two (28.5%) found significant main effects of RSA reactivity in depression (or depressive symptoms) in different directions among clinical (Pang & Beauchaine, 2013) and high-risk youth (Gentzler et al., 2009). However, four of the remaining five studies (80%) found significant interactive effects of RSA reactivity on depression with other physiological, behavioral, or environmental measures (discussed below).

3.5.1. Depressive Disorders—Two of the seven studies examined RSA reactivity among youth with clinical depression compared to other disorders and healthy controls. First, Pang and Beauchaine (2013) evaluated RSA reactivity among children with clinical depression compared to those with conduct disorder, comorbid conduct and depression, and healthy controls. In contrast to studies of adults with clinical depression, depressed children experienced *greater* RSA reactivity (e.g., greater decreases in RSA) in response to a sad film clip compared to those with only conduct disorder or healthy controls, with the comorbid group demonstrating the greatest RSA reactivity. The second study by Crowell and colleagues (2014) examined depressed adolescent girls (with and without self-injurious behaviors) compared to healthy adolescent girls in a 10-minute conflict discussion task with their mothers. In contrast to other studies of RSA reactivity, this study examined group differences in moment-to-moment RSA reactivity to the stressor in relation to aversiveness, defined by the extent of coercive or attacking utterances. This study did not report main effects of RSA reactivity on depression, but found that depressed female adolescents 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 (or had more positive utterances) 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. These studies are in contrast to most adult studies indicating that blunted reactivity is associated with depression, but also highlight the importance of examining behavioral regulation and momentary RSA patterns. It is important to note, however, that both studies included relatively small samples of 28 depressed children (Pang & Beauchaine) and 50 depressed adolescents (Crowell et al., 2014); therefore, more research with clinically depressed youth samples are needed to replicate these findings with larger samples and similar lab stressor tasks.

3.5.2. High-Risk Youth—Three studies evaluated RSA reactivity among children and adolescents at risk for depression using a longitudinal framework (Gentzler et al. 2009; Morgan et al., 2013; Yaroslavsky et al., 2014). Two of these studies operationalized high-risk youth based on a maternal history of depression (Gentzler et al., 2009; Yaroslavsky et al., 2014), whereas Morgan and colleagues (2013) included boys (ages 9-12) at risk for depression based on low socioeconomic status. Of these, only one study found evidence of a significant main effect of RSA reactivity on depressive symptoms (Gentzler et al., 2009), finding that children (ages 6-13) with reduced RSA reactivity to a sad film clip had greater clinician-reported depressive symptoms at the subsequent visit (on average 437.5 days later). Interestingly, this was not mediated by maladaptive emotion regulation, which was unrelated to RSA reactivity (Gentzler et al., 2009).

Although Yaroslavsky and colleagues (2014) did not find a main effect of RSA reactivity on the trajectory of depressive symptoms across the high- and low-risk youth (ages 8-14 years) or that RSA reactivity differed by risk status, they did have significant findings related to atypical RSA patterns. In particular, 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 offspring's RSA reactivity (but not resting RSA), and atypical RSA patterns were more prevalent among high-risk youth with formerly depressed mothers. These findings suggest that physiological regulation and reactivity to stress may be one mechanism of familial transmission of depression. In addition, in a three-wave longitudinal study of 160 at-risk boys from ages 12-15 (26% with maternal depression history), 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 at age 12 did predict depressive symptoms three years later (age 15), such that boys who had less RSA reactivity in a "hot topics" discussion with parents and more social withdrawal reported the greatest depressive symptoms in mid-adolescence. These findings indicate the importance of considering other risk factors and vulnerabilities, such as maternal depression and interpersonal behaviors, in conjunction with atypical RSA reactivity.

3.5.3. Community Samples—Two studies conducted by El-Sheikh and colleagues (2001; 2013) evaluated RSA reactivity among community samples of children in the context of environmental stress (i.e., marital discord). In the first study, RSA reactivity to a social stressor (listening to audiotaped segments of adults arguing) did not significantly predict depressive symptoms. However, in a subsequent study, El-Sheikh and colleagues (2013) found that there were no main effects of RSA reactivity to social stressor on depressive symptoms, but did find evidence of a four-way interaction between RSA reactivity, sympathetic reactivity (as measured by skin conductance), marital discord, and sex. Specifically, girls with higher RSA reactivity and lower sympathetic response experienced the highest levels of depressive symptoms across time, but only if they came from a home with higher levels of marital conflict. However, girls with reduced RSA and SNS reactivity experienced increasing depressive symptoms over time, with the highest depressive symptoms at age 10. The authors suggest that greater RSA reactivity may be generally adaptive for responding to stress; however, it may be important to consider the context and environment in which these youth are generally exposed, such that greater reactivity among youth exposed to more chronic stressors may be more maladaptive for depression.

4. Discussion

The present review highlights the current research on individual differences in *reactivity* of HRV in response to laboratory stressors in current and remitted clinical depression and depressive symptoms among adults and youth. Given the focus of theories on cardiac vagal control and regulation (Porges, 1995; Thayer & Lane, 2000), most research has focused on non-invasive measures of the PNS and vagal withdrawal in depression, specifically high-frequency (HF-HRV) or respiratory sinus arrhythmia (RSA). In short, these findings confirm

a significant role of the physiological stress response (RSA or HF-HRV), particularly that individuals with clinical depression 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, limiting conclusions regarding these measures. Although three prior meta-analyses of HRV and depression found that depressed adults and adolescents demonstrated lower resting HRV levels than controls (Kemp et al., 2010; Koenig et al., 2016; Rottenberg, 2007), the present review highlights the complexities of HRV reactivity in depression.

Among adults, the most consistent associations of HRV reactivity with depression occur for current clinical depression, with most studies (82%) finding that depressed individuals demonstrated atypical RSA reactivity compared to a healthy control group or predicting poorer depression recovery. However, two studies indicated that amplified RSA (increases in RSA) to the stressor also were characteristic of those with current depression (Liang et al., 2015; Rottenberg et al., 2007), suggesting that current depression may be characterized by atypical reactivity including both blunted and amplified RSA reactivity. Findings among adults with remitted depression were somewhat less positive for main effects, with all studies 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 and predominantly observed in current depression. In addition, less than 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 reactivity). However, a series of studies may shed some light on the variability of HRV findings, suggesting 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 predicted depressive symptoms (Yaroslavsky et al., 2013a; 2013b, Yaroslavsky et al., 2014), as well as in at-risk youth (Yaroslavsky et al., 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 HRV *reactivity* in depression risk.

Empirical research on HRV reactivity associated with depression among children and adolescents yields similarly inconsistent findings, with only two (28.5%) studies demonstrating main effects of RSA reactivity, but in different directions, such that greater RSA reactivity was found among clinically depressed adolescents (Pang & Beauchaine, 2013) and blunted RSA reactivity predicted increases in depressive symptoms among youth at high-risk based on maternal depression history (Gentzler et al., 2009). However, most 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. Greater RSA reactivity (in combination with lower sympathetic reactivity, greater marital conflict, or more aversive behavior) predicted depression status or symptoms (Crowell et al., 2014; El-Sheikh et al., 2013), whereas boys with greater social withdrawal and blunted RSA reactivity experienced the greatest depressive symptoms over time (Morgan et al., 2013). 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 (Yaroslavsky et al., 2014), 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 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, most 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 depression. Given the relatively early status of this research, there are a number of methodological considerations to be discussed and important avenues for future research. Thus, we conclude by proposing potential mechanisms in need of investigation.

4.1 Stressor Task

The variability in the types of stressor task used to induce psychological stress makes it 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 stressor that cues safety or positive social engagement should be associated with the activation of the vagal brake (or increased RSA) according to polyvagal theory (Porges, 1995), whereas a laboratory stressor that cues threat should elicit vagal withdrawal or decreases in RSA (HF-HRV). However, cognitive and social stressors are active stressors that involve self-relevant or social-evaluative threat (Schwerdtfeger & Rosenkaimer, 2011), whereas emotion-inductions are passive stressors designed to elicit specific emotions. Even among the social stressors, there is also variability, with some speech tasks requiring participants to defend themselves to law enforcement (e.g., Bylsma et al., 2014) or to have heated discussions with a parent (Morgan et al., 2013), which also may elicit differential stress levels among individuals. 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 social stress task, whereas the majority of youth studies 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), as well as developmental differences in the impact of stressors (Hollenstein et al., 2012). 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. Surprisingly, results did not appear to differ based on whether the study design included cognitive, social, or emotion-induction tasks, but more studies are needed to empirically evaluate stressor-specific responses.

Further, given concern that laboratory 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 HRV in response to naturally-occurring stressors in the context of depression. However, a recent study examined ambulatory HRV, social interactions, and symptoms of depression (Schwerdtfeger & Friedrich-Mai, 2009), finding that lower levels of HRV marginally predicted daily depressed mood, which differed based on the intimacy of social interactions. Thus, examining HRV reactivity to both laboratory 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.

4.2 Longitudinal Study Design

Perhaps one of the most glaring issues of study design included in the current review is the lack of longitudinal studies, particularly among adult samples. With the exception of two adult studies of depression recovery, all adult studies were correlational and did not longitudinally examine the effects of HRV reactivity on depression. Future research could 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 based on diagnosis alone, inasmuch as there is considerable heterogeneity in depression. Further, it would be particularly informative to examine HRV reactivity as a potential marker of risk for depression among vulnerable individuals, as indicated by indices of risk such as genetic risk, familial history, or even prior history of depression. Although several youth studies have focused on high-risk youth (Gentzler et al., 2009; Yaroslavsky et al., 2014), this has yet to be conducted among adult samples. In particular, studies examining individuals 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 a contributor to future depression risk.

4.3 Developmental Influences

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 studies demonstrating that there are normative developmental increases in RSA reactivity across childhood and adolescence (Hinnant et al., 2011; Pang & Beauchaine, 2013). Although patterns of HRV reactivity may remain somewhat stable over time (Hinnant et al., 2011; Salomon, 2005), there is also considerable evidence of the continued development of the stress response (Hollenstein et al., 2012) and certain environmental experiences may influence its development and increase risk for atypical HRV reactivity (e.g., Morgan et al., 2013).

In addition, there also are changes in the responsiveness of the physiological system to different stressors from childhood to adolescence (Obradovic, 2012), such that HRV reactivity to social stressors may be particularly important in depression risk during

adolescence (Stroud et al., 2009). Further, biological and pubertal changes during adolescence alter physiological responses to stress both directly and indirectly through its effects on the prefrontal cortex (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. 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 when atypical patterns of HRV reactivity confer greatest risk for depression. Of note, there are surprisingly few studies examining HRV reactivity and depression among adolescents, which represents an important avenue for future research to investigate given the developmental changes and increasing risk for depression during this time (Hankin et al., 1998).

4.4 Sex differences

Given that sex differences have been observed in HRV (Chambers & Allen, 2007) and the higher 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 higher resting levels of RSA than men (Chambers & Allen, 2007) 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 et al., 2013b). However, many studies included only females (Ahrens et al., 2008; Cyranowski et al., 2011; Nugent et al., 2011; Rottenberg et al., 2003; Yaroslavsky et al., 2013a; Yaroslavsky et al., 2014), only males (Liang et al., 2015; Morgan et al., 2013), or samples too small to reliably examine sex differences in these relationships. Several studies could have examined sex differences based on the equal inclusion of men and women or larger sample sizes, but these studies solely covaried the potential effects of sex rather than examine it as a moderator (Bylsma et al., 2014; Yaroslavsky et al., 2013b). Nonetheless, a few adult studies have examined sex differences in HRV reactivity and depression symptoms among undergraduate or community samples. In general, these studies have not found sex differences in these processes among adults (Gordon et al., 2012; Hughes & Stoney, 2000; Matthews et al., 2005).

Youth studies have examined sex differences; however, the only adolescent study of clinical depression included females only (Crowell et al., 2014), and a longitudinal study from childhood to adolescence included only at-risk boys (Morgan et al., 2013). Two studies of middle childhood showed mixed findings, with one demonstrating no differences between boys and girls (El-Sheikh et al., 2001) and one finding that girls with increasing RSA and decreasing SNS response to the lab stressor reported greater depressive symptoms than boys with similar patterns (El-Sheikh et al., 2013). Overall, more systematic analyses of sex differences in adult and youth studies are needed, particularly during the adolescent period and among those with current or remitted clinical depression. Future research should examine potential sex differences in HRV reactivity to different stressors, given research that women have greater physiological reactivity to social stressors than men, particularly during adolescence (Stroud et al., 2009).

4.5 Curvilinear Models

Importantly, our review indicates that whether *greater* HF-HRV reactivity (either withdrawal/decreases or amplification/increases) or *blunted* HF-HRV reactivity (attenuated withdrawal/response) is indicative of depressed state or risk for depression varies across studies. Thus, a possible explanation for these seemingly contradictory findings may be that moderate HRV reactivity is the most adaptive (Lovallo, Farag, Sorocco, Cohoon, & Vincent, 2012). For instance, it is possible that both hypo- and hyper-reactivity may be maladaptive depending on the 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 both lower and higher resting RSA exhibited greater depressive symptoms (Kogan, Gruber, Shallcross, Ford, & Mauss, 2013). A similar pattern also may be present for RSA reactivity (and other indices of HRV), with both hyper- and hypo-responses indicative of greatest depression risk. None of the studies in this review examined these patterns of HRV reactivity, which will be important for future research.

4.6 Environmental Context

Another important consideration in the examination of HRV reactivity and depression is environmental context. Several studies included in this review found significant influences of environment (e.g., trauma history, conflict in the home) on the association of HRV reactivity with depression (Cyranowski et al., 2011; El-Sheikh et al., 2013).

For instance, depressed women with a pronounced trauma history exhibited greater blunted reactivity to the speech stressor than non-depressed women or depressed women without a trauma history (Cyranowski et al., 2011). Similarly, although no known study specifically evaluated childhood (or adolescent) adversity or trauma and HRV reactivity within depression, a recent study by McLaughlin, Alves, and Sheridan (2014) found that childhood adversity predicted greater internalizing symptoms among adolescents with reduced RSA reactivity to a speech stressor. These findings are not surprising given research that trauma exposure impacts the limbic systems of the brain (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 (Lovallo et al., 2012; MacMillan et al., 2009). Adversity in the form of other environmental influences, such as stressors associated with low socioeconomic status (Evans et al., 2013; Morgan et al., 2013) and maternal depression (Gentzler et al., 2009; Yaroslavsky et al., 2014), also may contribute risk for blunted HRV reactivity and elevated depressive symptoms (Yaroslavsky et al., 2014). Thus, further evaluation of potential environmental influences is needed, which may significantly impact patterns of HRV reactivity and its relationship to depression.

4.7 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 this review, 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 atypical HRV reactivity. However, we propose 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 dysregulated HRV reactivity. One potential mechanism that could explain this transactional relationship may be the influence of HRV reactivity on the occurrence of stress. Specifically, we propose that stress may alter HRV response, and 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 emotionally, cognitively, or physiologically 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 (Hammen, 1991). 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 and even among those with underlying vulnerabilities beyond the effects of depressive symptoms (for a review, see Liu & Alloy, 2010). These stressors, in turn, predict depressive symptoms, as well as the onset, maintenance, and recurrence of depression.

Theories and research linking HRV reactivity to various neural regions, such as the amygdala and ventromedial prefrontal cortex (Porges, 1997; Thayer & Lane, 2000; Thayer et al., 2012), indicate that HRV is associated with emotion intensity, regulation, and responding (Appelhans & Luecken, 2006; Thayer et al., 2012). Additionally, HRV is also linked with deficits in executive functioning and control, including attentional and memory processes (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, Kubiak, Siewert, & Weber, 2013), potentially eliciting subsequent stressors. In addition, dysregulated HRV reactivity has been associated with neuroticism, considered to be a trait measure of stress and emotional reactivity (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 et al., 2013a). Although these vulnerabilities may not directly lead to stress, they may result in ineffective coping strategies for stress or behaviors that are poorly received by others, resulting in greater interpersonal stressors. HRV also is associated with maladaptive behaviors, including reduced interpersonal warmth (Diamond & Cribbet, 2013), poor social skills (Blair & Peters, 2003),

social disengagement and withdrawal (Geisler et al., 2013), and impulsivity and hostility (Beauchaine, 2001). These behaviors have been implicated in the stress generation process among adolescents and adults (e.g., McLaughlin & Nolen-Hoeksema, 2012; Uliaszek et al., 2010), which further exacerbates current depression or risk of future depression (Liu & Alloy, 2010).

A recent study provides preliminary evidence for the relationship between RSA reactivity and heightened stressors, finding that lower RSA reactivity predicts more daily negative interactions in couples (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 dysregulated reactivity. Further, different patterns of reactivity, including blunted 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.

4.8 Conclusion

Although this systematic review suggests that atypical HRV reactivity is implicated in depression, numerous questions remain. 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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Highlights

- Blunted reactivity of HRV may be associated with current depression in adults
- Further testing is needed for HRV reactivity among youth and adults with subthreshold and remitted depression
- Studies indicate the importance of contextual factors in the HRV reactivity- depression link
- Further research is needed to examine development, sex and curvilinear patterns
- Transactional Model of HRV Reactivity to Stress and Depression is proposed

Table 1

Adult Studies of HRV Reactivity in Current Depression

Authors	Year	N	N (% MDD)	Comparison	N (%) Female	Mean Age	HRV measures	Stressor Task	Major Findings
Bylsma et al. *	2014	119	49 (43%)	Control rMDD (N = 24)	89 (75%)	29.96	RSA	Social	Blunted Reactivity in MDD; *No differences between rMDD and control or rMDD and MDD
Cyranowski et al.	2011	30	15 (50%)	Control	15 (100%)	29.83	RSA	Social Emotion	MDD = Lower RSA in emotion task; MDD with trauma have lowest RSA to speech
Ehrental et al.	2010	50	25 (50%)	Control	34 (68%)	27.62	HF	Cognitive Emotion	Blunted HF-HRV Reactivity in MDD to combined stressor
Liang et al.	2015	210	160 (76%)	Control	0 (0%)	24.84	HF, LF, LF/HF	Cognitive	Reverse patterns of HF, LF, and LF/HF to stressor than controls (MDD= Increases in RSA and decreases in LF, LF/HF)
Nugent et al.	2011	17	10 (59%)	Control	17 (100%)	32.18	HF, LF, LF/HF	Cognitive	No significant main effects
Panaite et al.	2016	37	37 (100%)	N/A	31 (83.8%)	30.41	RSA	Emotion Social	Blunted RSA reactivity to sad film predicted MDD symptoms 6 months later and slow recovery (sad film and speech)
Rottenberg et al.	2003	56	25 (45%)	Control	56 (100%)	32.70	RSA	Emotion	Blunted RSA reactivity in MDD; No effect of crying on RSA reactivity for MDD
Rottenberg et al.	2005	55	55 (100%)	N/A	37 (67%)	33.94	RSA	Emotion	Blunted RSA reactivity predicted less recovery from MDD 6 months later
Rottenberg et al.	2007	50	25 (50%)	Control	37 (74%)	31.66	RSA	Social Cognitive	Significant differences between MDD and control; RSA increases in MDD
Shiuba et al.	2014	89	22 (32%)	Control	38 (55%)	40.32	HF LF/HF	Cognitive	Blunted HF and LF/HF ratio reactivity, among MDD
Yaroslavsky et al. *	2014	70	27 (39%)	Control rMDD (N = 14)	70 (100%)	30.01	RSA	Emotion	No significant main effects; Significant atypical patterns in current MDD and rMDD *

Note.

* = Studies that also included remitted depression;

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. Atypical Patterns = High Resting RSA + RSA augmentation; Low resting RSA + RSA withdrawal.

Table 2

Adult Studies of HRV Reactivity in Remitted Depression

Authors	Year	N	N (% rMDD)	Comparison	N (%) Female	Mean Age	HRV	Stressor Task	Major Finding
Ahrens et al.	2008	39	22 (52%)	Control	42 (100%)	52.52	HF, LF, LF/HF	Social Cognitive	No main effects
Yaroslavsky, Bylsma, et al. *	2013a	149	74 (50%)	Control	149 (100%)	27.95	RSA	Emotion	No main effects; Significant atypical patterns (resting RSA $\times$ RSA reactivity) predicted more depressive symptoms
Yaroslavsky, Rottenberg et al. *	2013b	206	114 (55%)	Control	152 (74%)	27.34	RSA	Emotion	No main effects; Significant atypical patterns (high resting RSA and greater RSA reactivity) in rMDD and predicted greater depressive symptoms

Note.

* = Study includes both remitted depression and depressive symptoms tables;

rMDD = Remitted Major Depressive Disorder; HRV = Heart Rate Variability; RSA = Respiratory Sinus Arrhythmia; HF = High Frequency; LF = Low Frequency. Atypical Patterns = High Resting RSA + RSA augmentation; Low resting RSA + RSA withdrawal.

Table 3

Adult Studies of HRV Reactivity and Depressive Symptoms

Authors	Year	N	N (%)	Female	Mean Age	HRV Measures	Stressor Task	Major Finding
Benvenuti	2015	54	48 (89%)		21.65	RSA rMSSD	Emotion	Blunted RSA and rMSSD reactivity to positive mood induction (but not sad) among those with elevated depressive symptoms
Gordon et al.	2012	199	118 (59%)		41.10	HF, LF/HF	Social	No significant main effects
Hughes & Stoney	2000	53	28 (53%)		18.70	HF	Cognitive	Greater HF-HRV reactivity in those with depressed mood
Matthews	2005	91	45 (49%)		18-50 *	RSA	Emotion	No significant main effects
Shinba et al.	2008	43	12 (28%)		31.10	HF LF/HF	Cognitive	Lower HF-HRV found among those with depressed mood
Silvia et al.	2014	131	85 (65%)		19.37	RSA	Cognitive	No significant main effects

Note.

* = No mean age given;

HRV = Heart Rate Variability; RSA = Respiratory Sinus Arrhythmia; HF = High Frequency; LF = Low Frequency. Atypical Patterns = High Resting RSA + RSA augmentation; Low resting RSA + RSA withdrawal.

Table 4

Child and Adolescent Studies of HRV Reactivity in Depression

Authors	Year	N	N (% MDD)	Comparison	N (% Female)	Mean Age	HRV Measures	Stressor Task	Major Finding
Clinical									
Crowell et al.	2014	75	50 (75%)	Control	75 (100%)	16.10	RSA	Social	Depressed group had greater RSA reactivity when they were more aversive
Pang & Beauchaine	2013	207	28 (14%)	CD, MDD + CD, Control	N/A	9.90	RSA	Emotion	Greater RSA reactivity in MDD (Greatest in comorbid CD and MDD)
High-Risk									
Gentzler et al.	2009	65	39 (60%)	N/A	30 (46%)	7.93	RSA	Emotion	Blunted RSA reactivity predicted more clinician-rated depressive symptoms
Morgan et al.	2013	160	1.9% (12) 8.6% (15)	N/A	0 (0%)	12-15	RSA	Social	Age 12 Low RSA reactivity and High Social Withdrawal predicted depressive symptoms at age 15
Yaroslavsky et al.	2014	97	48 (50%)*	Low Risk	51 (53%)	6.70	RSA	Emotion	No main effects; Atypical patterns of RSA reactivity predicted depressive symptoms; High Risk youth more likely to have atypical RSA reactivity
Community									
El-Sheikh et al.	2001	75	N/A	N/A	36 (48%)	9.90	RSA	Social	RSA reactivity did not predict depressive symptoms
El-Sheikh et al.	2013	251	N/A	N/A	128 (51%)	8.23	RSA	Social	Girls with blunted RSA, SNS reactivity, and high marital discord predicted greater depressive symptoms

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; SNS = Sympathetic Nervous System; Atypical Patterns = High Resting RSA + RSA augmentation; Low resting RSA + RSA withdrawal.