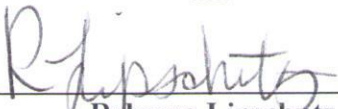


**TRAJECTORY OF RESPIRATORY SINUS ARRHYTHMIA ON RESTING AND
REACTIVITY MEASURES OF HEART PERIOD AND RSA BEFORE AND
AFTER CBT IN CHILDREN WITH PTSD**

AN ABSTRACT

**SUBMITTED ON THE FIFTEENTH DAY OF APRIL 2015
TO THE NEUROSCIENCE PROGRAM
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
OF THE GRADUATE SCHOOL
OF TULANE UNIVERSITY
FOR THE DEGREE OF
MASTERS OF SCIENCE**

BY

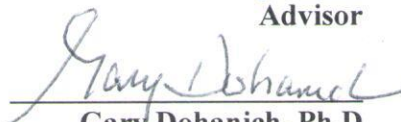


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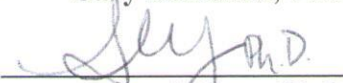
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Abstract

Although it is suggested that a dysfunctional stress response system may be associated with posttraumatic stress disorder (PTSD) the neurobiological underpinnings are not well established, especially in children. There is also limited research on how treatment for PTSD may impact associated physiology. Respiratory sinus arrhythmia (RSA) is a reliable measure of parasympathetic stress reactivity, and both resting RSA and RSA reactivity are physiological indicators related to children's emotion functioning and regulation. The present study examined if pretreatment resting RSA levels predicted RSA reactivity at pretreatment and the trajectory of resting RSA, RSA reactivity, resting heart period (HP) and HP reactivity after Cognitive Behavioral Therapy (CBT). Forty-nine children who experienced at least 1 traumatic event and presented with PTSD symptoms were assessed for psychological measures, RSA and HP at pretreatment, post treatment and a 3-month follow up. At pretreatment, lower resting RSA was associated with increased RSA withdrawal. Analysis with repeated measures mixed models indicated that lower resting pretreatment RSA and lower RSA withdrawal increased during CBT, and individuals with higher resting RSA and RSA withdrawal decreased during CBT, so that those at the extreme ends of higher and lower indices converged in the middle by the end of treatment. These data suggest an optimal moderate range for resting RSA and RSA reactivity. There were also significant gender differences on RSA reactivity after CBT. Lower pretreatment resting RSA predicted lower resting heart period (higher heart rate) across all time points but did not change with CBT. Pretreatment resting RSA did not predict HP reactivity. Post hoc analysis also revealed that PTSD symptoms were significantly reduced after CBT but this change was not associated with pretreatment resting RSA levels. Overall, these results suggest that children may change physiologically after CBT and the direction of the changes may depend on initial resting RSA levels.

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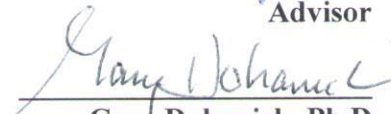


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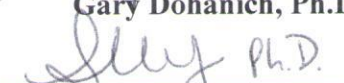
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Introduction

Exposure to a potentially traumatic event can lead to the development of posttraumatic stress disorder (PTSD), which includes symptoms of re-experiencing the trauma, avoidance behaviors, and alterations in cognition and mood, and alterations in arousal and reactivity (American Psychiatric Association, 2013). In particular, the symptoms of chronic increased arousal (i.e., exaggerated startle and hypervigilance) and heightened reaction to trauma reminders suggest a dysfunctional physiological stress system. Scheeringa, Zeanah, Myers and Putnam (2004) found that even minimally symptomatic young children have altered psychophysiological reactivity compared with non-traumatized children. Numerous studies have identified abnormal autonomic control of cardiac function (Cohen et al., 1997; Keane et al., 1998) in individuals with PTSD. Based on many early studies, it is widely assumed that subjects with PTSD have overactive sympathetic cardiac control with elevated baseline heart rates (HR) (Buckley & Kaloupek, 2001) and over-reactivity in response to stress (McFall, Murburg, Ko & Veith, 1990; McNally et al., 1987). It has been noted however that these studies lack resolution to separate overactive sympathetic effects from underactive parasympathetic effects, and finer grained measures would help to better understand the underlying mechanisms and strengthen interventions (Hopper, Spinazzola, Simpson & Van, 2006). Better understanding these processes could help identify adaptations of our neurobiological systems after exposure to potentially traumatic events and who might be most susceptible to PTSD, which could lead to more targeted interventions.

Respiratory Sinus Arrhythmia

Recent literature has focused on the importance of the parasympathetic branch over the sympathetic branch, because it is able to independently modulate resting HR and HR reactivity (Hopper et al., 2006). Respiratory sinus arrhythmia (RSA) is a reliable index of parasympathetic stress reactivity and measures high-frequency heart period variability (HF-HPV) which is linked to heart period oscillations during the normal respiratory cycle controlled by the vagus nerve. Parasympathetic activity can be measured from power spectral analysis for the corresponding age-appropriate frequency band (Grossman, Karemaker, & Wieling, 1991; Mezzacappa, Kindlon, Earls, & Saul, 1994). RSA has been observed as a valid measure of tonic parasympathetic activity and phasic changes (e.g. Grossman et al, 1991). Due to slightly different measurement methods in different studies, this parasympathetic index has been referred to as RSA, vagal tone, or HF-HPV. The vagal nerve influence on the heart is thought of as a brake and the most rapid regulator of the heart rate. Conceptualizing RSA as the “vagal brake” is a useful analogy for understanding its complex activity but may not be a comprehensive explanation. Absent the influence of the vagal nerve, the cardiac pacemaker naturally creates a heart rate of approximately 120 beats per minute. During restful times, vagal nerve activity acts as a brake to slow down heart rate and also to increase the variability of heart rate whereas during stressful times, the vagal brake is disengaged which leads to an increase in heart rate. Heart rate variability is almost entirely determined by this parasympathetic vagal process, whereas heart rate is much more a combination of parasympathetic and sympathetic influences.

Polyvagal theory is one of the most influential models in differentiating and understanding resting RSA levels and RSA reactivity or change in RSA from resting baseline to a stressor. (Porges, 1995, 2003a, 2003b, 2007) Resting RSA represents an individual's potential responsiveness to the environment and ability to regulate emotional states. **Higher resting RSA** indicates more application of the vagal brake at rest working to decrease HR and increased heart rate variability, suggesting more flexibility in the autonomic nervous system to respond to the environment. There is substantial literature that consistently associates higher resting RSA with greater abilities to regulate stress responsivity, emotional arousal, and attention (e.g. Bornstein & Suess, 2000; Porges, Doussard-Roosevelt, Portales, & Greenspan, 1996; Stifter & Fox, 1990). **Lower resting RSA** indicates less application of the vagal brake at rest and decreased HR variability and has been implicated with the greater psychophysiological arousal observed in chronic stress activation and anxiety disorders (Friedman & Thayer, 1998, Kawachi, Sparrow, Vokonas, & Weiss, 1995, Yeragani et al., 1993).

Individual differences in regulating this vagal brake are measured by changes in RSA or vagal tone in response to stressful stimuli. Porges (2007) has proposed that vagal withdrawal (disengaging the vagal brake) during times of stress (i.e. decrease in RSA from resting to stressor) may be an adaptive response that permits an individual's biological system to make necessary preparations for a challenging or stressful context (i.e. increased HR and arousal). Blunted vagal withdrawal or an increase in vagal tone in response to stressful contexts may indicate a maladaptive response associated with poor outcomes. However, there is limited research testing Porges's hypothesis of vagal response to stress in individuals with PTSD, and especially children with PTSD. Thus it

is important to establish how resting RSA and RSA reactivity are related to PTSD, and whether the adult literature can be translated to pediatric populations. The following sections provide a review of the current state of research regarding HR and RSA in adults and children with PTSD and potential treatment outcomes.

Heart Rate and PTSD

Heart rate is influenced by a combination of sympathetic and parasympathetic influences (Mezzacappa et al, 2004). Because so many forces influence heart rate, researchers have not considered it a specific index of either the sympathetic or parasympathetic system and therefore is not the result of a single central nervous system center.

Despite the non-specificity of heart rate, it has been the main variable of cardiac function that has been assessed in studies of participants with PTSD. This was probably due to the preliminary nature of earlier studies and because heart rate is simple to measure and does not require additional software or technical equipment. Blanchard (1990) was one of the first researchers to draw attention to increased resting HR in veterans with PTSD compared to veterans without PTSD. Since then, many investigators have replicated the findings of increased resting HR in individuals with PTSD (e.g. Cohen et al., 1997, 1998, 2000; Orr et al., 1997, 2000, 2003; Pallmeyer, Blanchard, & Kolb, 1986; Rasmussen et al., 2000). However a major concern with these studies was that the elevated basal HR could be in response to the stress associated with laboratory or assessment situations (Prins, Kaloupek, & Keane, 1995). Thus, the patients with PTSD may have demonstrated increased HR response to the stressful environment rather than heightened baseline physiological activity. Buckley and Kaloupek's (2001)

comprehensive meta-analysis investigated cardiovascular activity in the PTSD population and found PTSD was associated with elevated basal HR relative to both trauma-exposed and non-trauma-exposed controls subjects. The elevated basal HR finding remained even when controlling for the influence of anticipatory anxiety or stress on the results.

However, a few studies assessing resting HR outside of laboratory or medical contexts failed to find differences between veterans with PTSD and combat-exposed controls.

(Beckham et al., 2003; Muraoka, Carlson, & Chemtob, 1998; Orr, Meyerhoff, Edwards, & Pitman, 1998)

In addition to increased resting HR, it is also believed that individuals with PTSD show heightened HR reactivity to stressors. Orr et al. (2003) and Pitman et al. (2006a) examined HR at baseline and in response to startling sounds in identical twins discordant for trauma exposure. They found that trauma-exposed individuals who had PTSD exhibited significantly greater HR to startling sounds compared to non-trauma-exposed siblings and trauma-exposed twins without PTSD. In the largest study by far of cardiac function in adults with PTSD, Keane et al (1998) found higher resting levels in veterans with PTSD during baseline and greater HR response to standardized and idiographic trauma-related cues compared to veterans without PTSD. A review by Zoladz and Diamond (2013) suggested “increased HR reactivity appears to be a symptom that develops as a consequence of the disorder rather than being a vulnerability factor that increases one’s risk for PTSD.”

Although the vast majority of the literature on HR and PTSD has been conducted in adults and specifically veterans, there are numerous studies conducted in children as well. Scheeringa et al. (2004) found that traumatized children had significantly increased HR

during reporting of their trauma independent of PTSD status. Saltzman, Holden, and Holahan (2005) found significantly higher HR in exposed children compared to nonexposed controls at baseline and immediately after an interview about traumatic events. However with nontrauma-related stressors, MacMillian et al. (2009) found no group differences in HR in maltreated children with or without PTSD and nontraumatized controls during a psychosocial stress task. This suggests that HR may be elevated in children with PTSD to exposure to trauma-related stimuli but not with nontrauma related stressors.

Resting RSA and PTSD

In terms of **resting RSA**, studies have found either no difference or lower RSA in adult PTSD subjects compared to non-PTSD subjects. In a series of studies by Cohen et al. (1997, 1998, 2000) with samples of 9 to 14 PTSD subjects, baseline autonomic hyperarousal was observed as lower resting HF-HPV relative to non-traumatized controls. Hauschidlt, Peters, Moritz, and Jelinek (2011) also found lower baseline HPV (not limited to high-frequency) in 26 PTSD subjects compared to 18 non-trauma exposed controls. In contrast, Sahar, Shaley, and Porges (2001) compared 15 PTSD subjects to 14 traumatized controls and found no differences at baseline in their measure of RSA. A review by Nagpal, Gleichauf, and Ginsberg (2013) found significant effect sizes showing reduced HF-HPV in PTSD compared to control subjects which are consistent with the idea that PTSD presents with tonic autonomic hyper-arousal associated with less application of the vagal brake.

Hopper et al. (2006) investigated the relation of parasympathetic (RSA) involvement with basal heart rate in a study of 59 adults with PTSD. Although a substantial proportion

of the individuals with PTSD did not exhibit elevated basal HR, the subgroup with elevated HR exhibited lower RSA compared to those with non-elevated HR. This supported the idea that there is a parasympathetic contribution independent of any sympathetic contribution to the cardiac dysregulation in PTSD and that not all individuals with PTSD show the same RSA and HR patterns (Van Der Kolk, 2006).

RSA Reactivity and PTSD

Reactivity assesses changes in response to stimuli and provides different information about stress responses than baseline measures. In terms of **RSA reactivity to trauma stimuli**, results have been more inconsistent. Contradicting studies have found either a non-reactive state or increased reactivity in PTSD subjects. In Cohen et al.'s (1998) study of 9 subjects with PTSD, they found that in response to 20 minutes of recounting their personal traumatic event, subjects with PTSD demonstrated no significant change in either HR or HF-HPV, indicating a lack of autonomic response in comparison to non-trauma controls. The authors reasoned that due to elevated autonomic expenditure at rest, PTSD patients were unable to mount additional autonomic responses in response to trauma cues. Limitations of this study however were the small sample and the unusually long 20-minute stimulus duration. Hauschildt et al. (2011) also found their PTSD group did not show differential HRV responses to affective conditions including trauma-related cues compared to controls. This also implied decreased parasympathetic reactivity and inflexible response regulation. Sack, Hopper, and Lamprecht (2004) measured RSA in individuals with PTSD (no comparison group) during baseline and a 2-minute traumatic script and found a significant decrease of RSA in response to the trauma script (and sustained HR increase) in response to the trauma script, suggesting significant

withdrawal of the vagal brake in response to stress. They also observed that subjects with PTSD that showed low RSA demonstrated sustained conditioned arousal.

Compared to the substantial literature on adult PTSD, there is limited research on psychophysiology in pediatric PTSD populations. Scheeringa et al. (2004) were the first to demonstrate the association between RSA reactivity and PTSD symptomology in children. They found that even minimally symptomatic 1- to 6- year-old children show altered RSA reactivity to a trauma-related reminder compared to non-traumatized controls, suggesting that traumatic events impact psychophysiological reactivity regardless of PTSD diagnosis. They also found that the children's RSA reactivity was affected differentially depending on caregiving context and level of PTSD symptomology. Kirsch, Wilhelm, and Goldbeck (2015) examined 6-to 17- years-old trauma-exposed children for psychophysiological measures in response to a neutral and a trauma-related script. They did not find differences in sympathetic or parasympathetic measures including RSA between groups with and without PTSD either at baseline or in response to a trauma-related script.

Model of Stress Response Reactivity

These inconsistent findings support the notion of multiple physiological manifestations of PTSD, with some individuals exhibiting greater autonomic dysregulation than others. Altered stress reactivity has usually been viewed as a maladaptive consequence of exposure to traumatic stress however recent theoretical models of stress responsivity explain different response patterns as developmentally adaptive in specific environments.

The biological sensitivity to context theory (BSC) developed by Boyce and Ellis (2005) and the adaptive calibration model (ACM) by Del Giudice, Ellis, and Shirtcliff (2011) both try to describe differences in individual stress response patterns. They both suggest a nonlinear relationship between exposure to stress and optimal levels of stress responsivity. They suggest that individuals who experience low levels of stress/ threat in their environment and individuals who experience severe stressors/ highly unpredictable environments in early childhood tend to develop heightened sensitivity and stress reactivity. Individuals with moderate levels of stress or threat in their environment are not as sensitive to their context and may develop blunted reactivity profiles as buffers against chronic stressors or less extreme environments (Boyce & Ellis, 2005; Del Giudice et al, 2011). These theories have not been investigated in a PTSD context, but could help explain the heterogeneity of findings in the PTSD literature.

These theoretical models appear to represent a conceptual step forward for a newer understanding of stress responses; however, none of the models discussed the possibilities of change during treatments. Treatment settings offer a controlled setting to examine how these stress responses can be altered. Next, we will discuss that perhaps a more comprehensive way to study complex manifestations of PTSD is to examine physiological measures in response to treatment in addition to baseline measures.

Physiological Changes associated with PTSD Treatment

In terms of **change associated with treatment**, there are limited and inconsistent studies examining how physiological measures change after cognitive behavioral therapy (CBT) or other treatments for PTSD. A study by Sack, Lempa, Steinmez, Lamprecht, and Hofmann (2008) found increased HRV after eye movement desensitization and

reprocessing treatment and Garakani et al. (2009) also found increased RSA after CBT in adults diagnosed with PTSD. Lindauer et al. (2006) observed heightened HR responses in individuals with PTSD compared to trauma-exposed controls without PTSD. After successful psychotherapy, HR responsivity in individuals with PTSD was significantly reduced and correlated positively with PTSD symptoms. In contrast, Mathewson et al (2013) found resting RSA was positively associated with anxiety symptoms in individuals who responded to CBT for social anxiety disorder, and resting RSA decreased across CBT sessions. However they suggest that unexpected decrease in RSA across sessions may reflect RSA withdrawal in anticipation of stressful testing procedures. They found that change in RSA was important for predicting changes in anxiety symptoms rather than baseline levels. As there is such limited and inconsistent research on physiological changes with psychotherapy, it is not clear what direction would be expected after treatment. Mathewson et al (2013) suggested that it is important to engage the parasympathetic system in interventions and that increasing parasympathetic regulatory capacity is a good target for treatments. However not all studies have demonstrated parasympathetic changes in response to treatment. For example, in one of the few pediatric PTSD studies to examine autonomic variables, Grasso and Simons (2012) found psychotherapy did not appear to influence acoustic startle reflex, heart rate response and skin conductance.

To summarize, a theoretical rationale and empirical evidence exist indicating decreased resting RSA and decreased RSA reactivity (relatively less withdrawal of vagal brake) to trauma-related- stimuli in PTSD. Within individuals with PTSD, the findings on RSA reactivity to stressful stimuli have also been inconsistent and there is limited

evidence about the changes in RSA associated with treatment. Also, little is known about possible moderating variables for RSA such as dissociation or depression symptoms. The majority of literature is also limited to adult subjects and less is known about how this may translate to pediatric populations. The identification of reliable and valid biological correlates of PTSD is an important first step toward predicting longitudinal course of symptoms, treatment response, and individualizing treatment approaches.

We used existing data from a randomized trial of CBT to treat PTSD in children (Scheeringa and Weems, in press) to examine several hypotheses. Hypothesis 1 explored whether pre-treatment resting RSA predicted the other RSA indices. **1a. Is pre-treatment resting RSA associated with pre-treatment RSA reactivity?** Based on the review by Graziano and Derefinko (2013), we hypothesize that at pretreatment lower resting RSA will predict less RSA reactivity compared to higher pre-treatment resting RSA as evidenced by a smaller decrease in RSA in response to the trauma stimuli. **1b. Does pre-treatment resting RSA predict the trajectories of resting RSA and RSA reactivity over the course of psychotherapy treatment?** Due to the absence of prior studies in youth with repeated measures of these indices during treatment, there are limited data to forecast the trajectories of resting RSA and RSA reactivity after cognitive behavioral therapy at post-treatment and follow-up. **Hypothesis 2: Does pre-treatment resting RSA predict the HP indices?** **2a. Is pre-treatment resting RSA associated with pre-treatment resting HP or HP reactivity?** Following Hopper et al. (2006) and Sack et al. (2004) we hypothesize that lower pre-treatment resting RSA will associate with lower pre-treatment resting heart period (increased baseline heart rate) and greater pre-treatment HP reactivity (greater decrease in HP / HR increases) in response to the

script as compared to higher pre-treatment resting RSA. **2b. Does pre-treatment resting RSA predict the trajectories of resting HP and HP reactivity over the course of psychotherapy treatment?** This study will be exploratory in investigating the differences in HP trajectories after treatment relative to higher and lower pre-treatment resting RSA. Based on previous treatment outcome studies (Blanchard et al., 2003; Lindauer et al, 2006) we hypothesize that at post-treatment and follow up, lower pre-treatment resting RSA will predict increased resting HP (decreased baseline HR) and decreased HP reactivity (less HR increase) in response to the trauma stimuli relative to their resting HP and HP reactivity at pretreatment.

Methods

Participants

Subjects for this study include 49 children, 7-13 years old ($M = 9.7$, $SD = 1.9$), who experienced at least one potentially traumatic event and presented with PTSD symptoms. Subjects were assessed for psychological symptoms and heart rate variability measures at pretreatment, post treatment and a 3-month follow up. Treatment includes completion of 12 weeks of cognitive behavioral therapy.

Seventy-eight participants were evaluated in lab and 51 were eligible and offered treatment. The other 27 were not eligible due to inclusion or exclusion criteria and most of the time this was because they did not present with enough PTSD symptoms. Eleven did not return for any therapy sessions. Forty-nine of the participants underwent heart assessment and demographic are presented in Table 1.

To be included in this study, children must have experienced or witnessed at least one life-threatening event, been 7 through 13 years old and presented with five or more PTSD symptoms plus functional impairment. Exclusion criteria included a Glasgow Coma Scale score of 5 or less in the emergency room, intellectual disability (ID) as indicated by standard scores below 50 on the Peabody Picture Vocabulary Test (this is a measure of verbal ability but was used in this study as a cost effective estimate of moderate ID), autistic disorder (from clinical observations by the principal investigator), blindness, deafness, and foreign language speaking families, suicidal, homicidal, or gravely disabled, concurrent counseling outside of the study, any kidney or liver ailment,

epilepsy or history of seizures and bipolar disorder or schizophrenia. Psychoactive medications were allowed as long as the dose had been stable at least four weeks prior to treatment and remained stable.

Measures

The Diagnostic Interview Schedule for Children-IV (DISC-IV) was used to determine number of PTSD symptoms for eligibility into the study. The DISC is the most broadly used diagnostic instrument for youth and the questions map in a very straightforward way on the DSM-IV criteria (Shaffer, Fisher, & Lucas, 2000). Given the established discordance between youth and parent reports of PTSD symptoms (Scheeringa et al. 2006), a joint rating was created using the either/or rule – if either the child or the parent endorsed a symptom, it was counted. Cronbach's alphas in this study were 0.87 for the youth ratings and 0.83 for the parent ratings.

The Child PTSD Symptom Scale (CPSS) was used to show change in PTSD severity over time. The CPSS is a self-administered measure of the 17 PTSD DSM-IV symptoms rated on a 4-point (0-3) likert scale (Foa, Johnson, Feeny, & Treadwell, 2001). This yields a broader range of scores that indicate intensity and frequency that may be more sensitive to change than number of PTSD symptoms. This measure was administered pre-treatment, post-treatment and at follow-up. Child and parent versions were used and a joint score was created using an either/or rule.

Heart Rate Variability Data Collection

Heart period (HP) and respiratory sinus arrhythmia (RSA) were collected using an electrocardiogram (ECG). Electrodes were placed axially on the left and right rib cage and centrally on the chest (Scheeringa et al., 2004). First, the ECG was recorded for a 1-

min baseline epoch while the child was instructed not to move or speak. The trauma stimulus was a 1-min script created by a clinician narrating each child's personal trauma based on what the child and parent described at intake. These narratives were recorded on a digital voice recorder and played to the child during the stimulus epoch. The HP between R waves was calculated on a computer program and mean HP for each time epoch was recorded.

HP reactivity was measured as change scores in response to trauma stimuli and was calculated by subtracting the mean HP for the preceding 1-min baseline from the mean HP for the 1-min trauma script stimuli. As shown in Figure 1, a **negative HP change score** indicates HP decreased in response to the stimuli (heart rate increased) and **positive HP change score** indicates HP increased in response to the stimuli (heart rate decreased).

RSA was estimated from power spectral analysis in the empirically validated respiratory frequency for the child's age (Scheeringa et al., 2004). Frequency bands of .2-.65 Hz were used for the children in this study. Mean RSA values were used from baseline and trauma script recordings and log transformed. To measure RSA reactivity, RSA change scores were calculated using the same method as HP change scores. As shown in Figure 1, a **Negative RSA change score** indicates that RSA decreased (vagal withdrawal, or relatively less application of the vagal brake) in response to the stimulus. A **positive RSA change score** indicates that RSA increased (vagal augmentation, or relatively more application of the vagal brake) in response to the stimulus.

Treatment

All children received individual cognitive behavioral therapy (CBT) treatment with a 12-session manualized protocol, Youth PTSD Treatment (YPT). YPT includes traditional components of CBT for pediatric trauma including psychoeducation, skill-building in identification and expression of feelings, relaxation exercises, exploration of negative thoughts, narrative processing of trauma events, graded exposure exercises in and out of the office, safety plans, and involvement of parents in every session. Therapy was delivered by two masters level therapists trained in CBT and supervised by the authors.

Data Analysis

To test hypothesis 1a, a bivariate correlation between pretreatment baseline RSA and pretreatment RSA reactivity was used. Because there are missing data from 21 subjects at follow up, hypothesis 1b used repeated measures mixed model analysis to test the trajectory of RSA baseline and reactivity.

Similar to above, a bivariate correlation was used to test hypothesis 2a to examine the association between pretreatment baseline RSA and pretreatment baseline HP and HP reactivity,. To test hypothesis 2b, separate repeated measures mixed models was also used to analyze the trajectories of baseline HP and HP reactivity.

Results

Preliminary Analysis

All predictor and outcome variables for all hypotheses were tested for association with age, gender, race, pretreatment PTSD severity, and time since trauma as shown in Table 2 and Table 3. Only variables that showed significant bivariate correlations were included as covariates in mixed model tests. Variables with no significant correlations were not included in the mixed models as covariates. Gender was included as a covariate in the testing the effects of resting pretreatment RSA on the trajectory of RSA reactivity, and PTSD symptoms were included as covariate in the test of resting pretreatment RSA on the trajectory on HP reactivity.

Hypothesis 1: Does pretreatment resting RSA predict resting RSA reactivity and RSA at future times?

Hypothesis 1a. Is lower pre-treatment resting RSA associated with less pretreatment RSA reactivity? Pretreatment resting RSA was negatively correlated with pretreatment RSA change ($r = -.597, p < .0001$). This suggests lower pre-treatment resting RSA (less application of the vagal brake at rest) was correlated with higher RSA change scores. Because the nature of the reactivity responses were generally in the direction of negative change scores (withdrawal of the vagal brake), it is also appropriate to frame this as relatively less RSA withdrawal in response to the trauma script. This was evidenced by relatively less negative RSA change scores closer to 0, which indicated a

blunted response, or a positive RSA change score indicating more application of vagal brake. Higher pre-treatment resting RSA was associated with greater decreases in RSA or relatively more RSA withdrawal in response to the trauma script. Figure 2 illustrates the directionality of these concepts.

Hypothesis 1b. Does Pre-treatment resting RSA predict the trajectories of resting RSA and RSA reactivity over the course of psychotherapy treatment? For the test of resting pretreatment RSA predicting resting RSA at post treatment and follow-up, there was significant interaction of resting pretreatment RSA by time, $F(2, 30) = 8.61$, $p = .001$, indicating that subjects resting RSA levels changed differentially over time with respect to varying levels of pretreatment resting RSA. The main effect of time was not significant, $F(1, 30) = 0.20$, $p = .66$. Figure 3 illustrates that those with higher resting RSA at pre-treatment tended to decrease their resting RSA over time, whereas lower resting RSA was associated with increases in resting RSA over time. Although the analyses were run as continuous variables, High and Low pretreatment resting RSA groups were created for visual purposes in the graphs. High and Low groups were created from the top and bottom 33% of resting RSA in the sample at pretreatment. Although it is more conventional to use ± 1 SD to compare groups at opposing ends, due to the small sample size, we chose to use top and bottom 33% so more subjects were included ($n=15$ for both groups at pretreatment).

There was a significant interaction between resting pretreatment RSA and time on RSA reactivity, $F(2,45) = 3.51$, $p = .04$ and significant main effect of time, $F(2, 45) = 3.63$, $p = .03$. There was no main effect of pretreatment resting RSA, $F(1,45) = 2.33$, $p = .13$. This suggests that RSA reactivity also changed differentially over time with

respect to varying levels of pretreatment resting RSA. Figure 4 illustrates that at baseline, subjects with high resting RSA also showed relatively more RSA withdrawal (mean change score of $-.33$), whereas subjects with low resting RSA exhibited less RSA withdrawal (mean change score of $.10$). Their lack of withdrawal was evidenced by either a blunted response or an increase in RSA. What was somewhat surprising was that both groups changed over time in different directions. Those with higher resting RSA at pre-treatment changed over time from relatively more negative reactivity (greater vagal withdrawal) to relatively less negative reactivity (relatively less vagal withdrawal). Those with lower resting RSA at pre-treatment changed in the opposite direction; they changed from relatively less negative reactivity (either blunted response or vagal augmentation) to more negative reactivity (Relatively more vagal withdrawal).

There was also a significant effect of gender on RSA reactivity at post treatment and follow up, $F(1,45) = 8.09, p < .001$. Post hoc analysis indicates that males showed more RSA withdrawal (mean RSA change score of -0.32 and $-.30$ at post treatment and follow up respectively) compared to females (mean RSA change score of -0.03 and 0.04 at post treatment and follow up respectively). The Wilcoxon Rank-Sum test indicated no significant difference between genders for RSA change at pretreatment, $W(n_{males}=28, n_{females}=20) = 514, p = .62$, however there was a significant difference between genders at post treatment $W(n_{males}=17, n_{females}=13) = 257, p = .02$ and follow up, $W(n_{males}=15, n_{females}=13) = 245.5, p = .01$. Figure 5 suggests that females tended to show a blunted RSA response even after CBT and males tended to increase their RSA withdrawal after CBT. As shown in Table 4, males showed more negative RSA change scores (more

vagal withdrawal) than females at post treatment and follow up regardless of pretreatment resting RSA.

Hypothesis 2: Does pretreatment resting RSA predict resting HP and HP reactivity?

Hypothesis 2a. Is lower pre-treatment resting RSA associated with decreased pre-treatment resting HP, and vice versa? Pre-treatment resting RSA was positively correlated with pre-treatment HP, ($r = .589, p < .0001$). Lower resting RSA was associated with lower resting HP, which indicates higher resting HR.

Hypothesis 2a. Is pre-treatment resting RSA associated with pre-treatment HP reactivity? There was no observed significant correlation between pretreatment resting RSA and HP reactivity, ($r = -.0516, p = .78$).

Hypothesis 2b. Is pre-treatment resting RSA associated with changes in resting HP or HP reactivity over the course of psychotherapy treatment? For the test of resting pretreatment RSA predicting resting HP over the course of psychotherapy, there was a main effect of resting pretreatment RSA, $F(1,46) = 16.07, p < .001$, but no time main effect or interaction effect, $F(2,46) = .07, p < .92$, and $F(2,46) = .07, p < .94$ respectively, suggesting that different levels of resting pretreatment RSA predicted different levels of resting HP, but these did not change after treatment. Figure 6 illustrates that subjects with high resting RSA exhibited significantly higher resting HP (lower resting HR) and subjects with low resting RSA exhibited low resting HP (high resting HP).

There was no observed significance of resting pretreatment RSA on the trajectory of HP reactivity, $F(1,45) = .03, p = .87$. There was also no observed significance for time,

interaction effect, or PTSD symptoms, $F(2,45) = .73, p = .49$, and $F(2,45) = .72, p = .42$, $F(1,45) = .44, p = .51$, respectively.

Figure 7 shows that HP reactivity appeared to change from decreased HP reactions at baseline to relatively less decreased HP reaction or increased HP reaction at post-treatment, but by the 3-months follow-up subjects had reverted to more decreased HP reactions so that there was no overall effect of time.

Post Hoc Examination of PTSD symptoms

Examining concurrent PTSD symptom outcomes was not the focus of this thesis but was added after the main results were analyzed as a very preliminary examination of symptom change in association with the physiology. As physiological differences were observed based on resting pretreatment RSA, high and low resting pre-treatment RSA groups (Top and bottom 33% of the sample, $n = 16$ for both groups) were created and tested for this preliminary analysis. PTSD symptoms were joint parent and child scores from the CPSS measured at pretreatment, post treatment and a 3-month follow-up. A repeated measure ANOVA was used to assess if PTSD symptoms changed after CBT and if there was a difference in PTSD symptom change between RSA groups. There was a significant main effect for time $F(2, 16) = 20.51, p < .0001$, indicating that PTSD symptoms were significantly reduced after CBT. However, the interaction between pretreatment resting RSA and time was not significant, $F(2, 16) = .18, p = .84$, suggesting that PTSD symptom reduction was not associated with pretreatment resting RSA. There was also no significant main effect between groups $F(1, 17) = .55, p = .47$. Figure 8 illustrates that both RSA groups showed similar levels of PTSD symptomatology at pretreatment as well as similar symptom reductions after CBT.

Discussion

This is the first known study to examine the associations between resting RSA, RSA reactivity, resting HP, and HP reactivity and how these measures change after CBT in children with PTSD. There were several important findings that may help to explain the conflicting and inconclusive findings on resting RSA and RSA reactivity in PTSD subjects and initiate a discussion on how they can change with treatment.

Resting RSA

Hypotheses 1a was supported, as pretreatment resting RSA was associated with pretreatment RSA reactivity. This is important data for understanding how the resting state of one of the main neurobiological stress response systems (resting RSA) is related to a situation that closely mimics the therapeutic activity of exposure exercises in CBT and also closely mimics the actual stress response (RSA reactivity). The data suggest that the direction of reacting and adapting to stressful situations is contingent on the resting baseline state.

Hypothesis 1b was exploratory to examine the ability of pretreatment resting RSA to predict the trajectories of resting RSA and RSA reactivity after CBT. Higher pretreatment resting RSA predicted a decrease in resting RSA after CBT whereas lower pretreatment resting RSA predicted an increase in resting RSA after CBT. Surprisingly, both groups trended toward a similar middle range of resting RSA at the 3 month follow up, suggesting an ideal middle range for resting RSA. This supports the idea that extremely high or low resting RSA may be maladaptive and a moderate resting RSA is optimal. (Kogan, Gruber, Shallcross, Ford, and Mauss, 2013)

Although RSA baseline is commonly thought to have a linear relationship with positive outcomes, (i.e., higher RSA baseline is better) other theories describe a quadratic relationship or “inverted U” shape, where moderate levels of RSA are optimal and extremely high RSA baseline levels may be evidence for “too much of a good thing” under certain circumstances (Kogan et al., 2013). In this sample, it is suggested that one subgroup of those with PTSD has an adaptive (or perhaps maladaptive) physiological response of elevated resting RSA, whereas another subgroup of those with PTSD has an adaptive (or maladaptive) physiological response of decreased resting RSA.

The implications for future assessment may include understanding the underlying factors that determine why there are subgroups with different physiological adaptations with the same PTSD phenotype. The implications for clinical treatment may include exploring how these different resting physiological patterns can be used to individualize treatment.

RSA Reactivity

As expected, those with higher pretreatment resting RSA showed larger decreases in RSA in response to a trauma-related stimulus at pretreatment (i.e., withdrawal of the vagal brake), and those with lower pretreatment resting RSA showed on average increases in RSA (i.e., application of the vagal brake). Over time, and ostensibly due to treatment, those with higher pretreatment resting RSA decreased the magnitude of change in RSA reactivity when presented with a trauma-related stimulus by moving from relatively more negative RSA reaction change scores to relatively less negative RSA reaction change scores (i.e., decreased the magnitude of withdrawal of the vagal brake over time). In contrast, those with lower pretreatment resting RSA increased the

magnitude of change in RSA reactivity in the other direction by moving from positive RSA reaction change scores to negative change scores (i.e., application of the vagal brake to withdrawal of the vagal brake). Most previous speculations have considered greater withdrawal of the vagal brake (decreased RSA) as the more adaptive physiological response to stress, but those have been limited mostly to cross-sectional studies. This high pretreatment resting RSA group in particular challenges those previous speculations because after treatment, they showed less withdrawal of vagal brake (less negative RSA change).

RSA reactivity also seemed to converge towards a middle range by the 3 month follow up, again suggesting an optimal moderate level of reactivity. The results from hypothesis 1 suggest that both excessive and reduced resting RSA and reactivity may be maladaptive and it may be best for the physiological indices to function somewhere in a moderate range. This is consistent with Marcovitch et al. (2010) who also found that children with moderate decreases in RSA outperformed children whose RSA decrease by too much or too little on executive functioning tasks. Children who fail to show vagal withdrawal may have difficulty reacting to environmental stressors whereas children with extremely high vagal withdrawal may be physiologically over-aroused (Marcovitch et al., 2010).

Since both high and low RSA patterns changed after treatment, it is difficult to infer if either RSA pattern is “better” or more adaptive. This provides evidence that is consistent with biological sensitivity to context theory (BSC) or adaptive calibration model (ACM) that adaptive or maladaptive physiological reactions may be person-specific and context-specific and it is unlikely that a certain physiological reaction has the

same effect or valence in all individuals in all situations. As these theories are not definitive models, our results can further help develop these theories and extend into a PTSD / traumatic stress population. Our findings of both high and low levels of reactivity are consistent with the theory suggested in ACM that severe or traumatic stress can develop into stress response patterns of either high or low reactivity. Due to the nature of our sample, we cannot determine what would be high or low reactivity compared to a non PTSD or non-traumatized sample, but this suggests that within PTSD samples there is great variability in resting RSA and RSA reactivity. Future studies should take this into account.

To further complicate the individual variability observed in RSA findings, our data suggests there may be gender differences that could moderate RSA reactivity. In this study, boys showed greater RSA withdrawal after treatment, and girls showed lower RSA withdrawal and even RSA augmentation in response to the trauma-related stimulus. This suggests that it may be more adaptive for boys to have higher RSA reactivity and for girls to have lower RSA reactivity. The current literature on gender differences on RSA reactivity in children is limited. Morales, Beekman, Blandon, Stifter and Boyce (2014) and Hinnant and El-Sheikh (2013) found similar results that girls who showed more RSA withdrawal were more likely to display externalizing or internalizing symptoms, whereas boys displayed similar symptoms if they showed low RSA reactivity or RSA augmentation. Obradovic, Bush, Stamperdahl, Adler, and Boyce (2010) also found that high RSA reactivity was related to positive outcomes for boys, but for girls low RSA reactivity was associated with the same positive outcomes. Hinnant and El-Sheikh suggested that for girls, showing high RSA reactivity during these tasks may be

maladaptive in certain contexts and indicate overarousal and dysregulation towards stressors. In contrast, boys who show a lack of physiological response predicted more psychopathology (Morales et al., 2014) which could indicate lack of engagement with stressor. A potential cause for these gender differences could include differences in how boys and girls interpret and cope with stressful situations (Morales et al., 2014). Taking these findings with our results suggests that different patterns of RSA reactivity may be more adaptive for girls versus boys and predict different psychopathology or symptomology.

This data also has clinical importance for understanding the physiological effects of psychotherapy and the individual differences observed. The limited research on psychophysiology and treatment in PTSD populations generally suggests low RSA at pretreatment and increased RSA after treatment (Garakani et al., 2008; Sack et al., 2008). One study examining RSA and CBT in social anxiety disorder (Mathewson et al., 2013) found that resting RSA decreased over time; however they attributed this to a habituation effect of their stimulus. Our results contribute to this body of literature by showing bidirectional RSA changes dependent on resting RSA levels at pretreatment.

PTSD Symptoms and Psychophysiological Outcomes

This is also the first study to examine psychophysiological and PTSD symptom outcomes in children after CBT. Considering the substantial differences between RSA measures at pretreatment it is somewhat surprising that there was no association with PTSD symptoms. However this is consistent with Scheeringa (2004) who found altered psychophysiological reactivity regardless of PTSD diagnosis. As both high and low resting pretreatment RSA groups showed similar CPSS scores at pretreatment and were

both able to show similar reductions in symptoms after CBT, it is difficult to interpret if either group was more adaptive or “better” before CBT. This provides evidence for multiple manifestations of PTSD that display different RSA patterns. Both RSA groups may have had different maladaptive RSA patterns at pretreatment, but our data suggest that CBT was able to concurrently reduce PTSD symptoms and change RSA patterns in opposite directions to meet at a middle range. The observation of similar significant reductions in PTSD symptoms strengthens the possible theory that moderate levels of resting RSA and RSA reactivity are optimal and associated with more positive outcomes.

These results also have important clinical implications. A key component of BSC is that some individuals show low responsivity to their environments “for better or worse” (Ellis, 2005). According to this theory, individuals who show low reactivity (such as our low RSA group) are less reactive to both stressful stimuli and positive stimuli such as treatment suggesting that they may not be able to respond as effectively to treatment. However in the present study, children who showed low resting RSA and less RSA withdrawal at pretreatment increased their resting RSA and RSA withdrawal and decreased their PTSD symptoms after CBT. Considering higher resting RSA and RSA withdrawal are associated with better emotion regulation, it is possible that the physiological changes in RSA observed with treatment, contributed to children’s potential responsiveness to CBT. Overall, regardless of RSA reactivity at pretreatment, children were seemingly able to respond to CBT at physiological and symptom levels.

Heart Period

Hypothesis 2a was supported as lower pre-treatment resting RSA was associated with decreased pre-treatment resting HP, and vice versa, however HP reactivity was not predicted. Pretreatment resting RSA values predicted pretreatment resting HP values as hypothesized and consistent with studies in adults. Only subjects with low resting RSA exhibited low resting HP indicating high resting HR. For example, Hopper et al. (2006) found that low resting RSA associated with increased resting HR in adult PTSD subjects, and that not all PTSD subjects demonstrate high resting HR. While this was not surprising because of the substantial influence of the parasympathetic system on HR, it is the first known demonstration of the relation in this pediatric PTSD population.

In the exploration of Hypothesis 2b, it was somewhat surprising that the HP indices did not change after CBT considering changes in resting RSA and reactivity. This supports that emotional regulation and improvement may best be seen in RSA changes not HP. This is important evidence for the value of measuring RSA as an index of the parasympathetic nervous system, as opposed to HP which is a less precise index that is influenced by both parasympathetic and sympathetic systems. The demonstrated ability of the parasympathetic nervous system to adapt and regulate the heart's response to stress makes it a valuable target for treatment.

In summary, taking the RSA and HP results together presents a complex picture with two distinct patterns at pretreatment. The children with low resting RSA seem to also exhibit a lack of RSA withdrawal as well as low resting HP (increased resting HR). The children with high resting RSA seem to also exhibit large RSA withdrawal and high resting HP. However, regardless of high or low resting RSA and RSA reactivity, the

children on average showed a large decrease in HP in response to the traumatic reminder (increased HR) at pretreatment. The patterns illustrate the importance of RSA in regulating heart rate and heart rate reactivity.

In the low resting RSA pattern there is less vagal brake present at rest to slow down HR so resting HR is increased. Since RSA levels (amount of vagal brake present) are already low at rest, when presented with stressful stimuli RSA may be unable to decrease further (unable to withdraw the brake any more), which could explain why either a blunted RSA reactivity pattern or increased RSA pattern is seen. This is consistent with what Cohen et al. (1999) observed. However, since there is very little vagal brake present to slow down and regulate the heart, heart rate is still able to increase in response to stress.

In the high resting RSA pattern there is much stronger influence of the vagal brake slowing down heart rate at rest. The higher levels of RSA (vagal brake) present at rest represent greater potential responsiveness and ability to regulate HR (Porges et al, 1996). In response to stress, the individual must disengage the vagal brake (RSA withdrawal) to allow their heart rate to increase, which explains both the large decrease in RSA and increase in HR observed.

Study Limitations

There are many noted limitations of the present study. Our sample did not include any control groups such as trauma-exposed without PTSD symptoms or non-trauma exposed. Therefore the observed high and low RSA measures were only relative within our sample. In examining potential treatment effects, it would have been ideal to control for placebo effect. This study also has a small sample size. The sample also

includes children in a large range of ages who may be in different stages of developmental processes. We also cannot conclude if the observed physiological patterns were maladaptive responses to exposure to traumatic events or present before exposure to traumatic events and contributed to susceptibility for psychopathology. The experimental setting and repeated testing procedures may have been a confounding effect. Since the children knew what to expect at the later time points, this may have differentially impacted the salience of the stressor. Some children may have been very anxious to repeat the testing while others may have habituated to the testing procedures. Having the research assistant in the room during the assessment may have decreased the perceived threat and contributed to low psychophysiological reactions (Coan, Schaefer, & Davidson, 2006) or the presence of this unfamiliar person may have increased their stress response. There are many other factors not analyzed that could have contributed to RSA patterns such as parenting context or environmental factors. Additionally as time since trauma was substantial for some subjects, this data indicates that the improvements may not have been natural and were a result of the treatment. However the large variability in the time since trauma and trauma history in our sample may have contributed to the observed heterogeneity in physiological responses.

Conclusions

In conclusion the current study contributes to our knowledge of psychophysiological correlates of PTSD in children and how these physiological measures may be impacted with CBT. This study is one of very few studies to examine RSA longitudinally in children. This is also the first known study to show how RSA can change differentially after CBT based on resting RSA at pretreatment. Taken with other

existing studies, it calls into question the generalizability of maladaptive physiological patterns observed and suggests multiple manifestations within PTSD populations which should be taken into consideration for future studies. It also contributes to the few studies that suggest optimal moderate levels of resting RSA and RSA reactivity.

Appendix

Table 1

Demographics of n=49 Participants Who Underwent Heart Assessment

| Characteristic | n or M | % or SD |
|---|--------|-------------|
| Males, n (%) | 28 | 57.1 |
| Females, n (%) | 21 | 42.9 |
| Race | | |
| Black, n (%) | 25 | 51 |
| White, n (%) | 18 | 36.7 |
| Mixed, n (%) | 6 | 12.2 |
| Age (year), mean \pm SD | 9.7 | \pm 1.9 |
| Maternal age (year) , mean \pm SD | 42 | \pm 12.2 |
| Maternal education (year), mean \pm SD | 14 | \pm 3 |
| Paternal age (year), mean \pm SD | 33.9 | \pm 18.2 |
| Paternal Education (year), mean \pm SD | 8.0 | \pm 8.9 |
| Father lives with child, n (%) | 9 | 8.4 |
| Primary type of Trauma | | |
| Natural disaster, n (%) | 6 | 12.2 |
| Witnessed domestic violence, n (%) | 14 | 28.6 |
| Attacked/beaten, n (%) | 2 | 4.1 |
| Sexual, n (%) | 11 | 22.4 |
| Threatened with weapon, n (%) | 1 | 2 |
| Bad accident, n (%) | 1 | 2 |
| Witnessed murder, n (%) | 4 | 8.2 |
| Seen dead body, n (%) | 10 | 20.4 |
| # types traumas - parent report, median (Range) | 2.0 | (1-7) |
| # types traumas - child report, median (Range) | 2.0 | (1-8) |
| PTSD Symptoms – Child + Parent score, mean \pm SD | 14.2 | \pm 8.5 |
| Days since last trauma, mean \pm SD | 804.6 | \pm 745.3 |

Table 2

Correlations Between Respiratory Sinus Arrhythmia (RSA) Variables and Demographics

| RSA Variable | Age | Gender | Race | Time Since Trauma | PTSD Symptoms |
|----------------|-------|--------|-------|-------------------|---------------|
| Resting RSA | | | | | |
| Pretreatment | -.073 | -.037 | -.253 | -.080 | -.056 |
| Post Treatment | -.060 | -.307 | -.246 | -.122 | .050 |
| Follow up | -.198 | -.235 | -.014 | -.336 | .222 |
| RSA Change | | | | | |
| Pretreatment | .052 | .073 | .046 | .206 | .264 |
| Post Treatment | -.048 | .431* | .216 | .020 | -.150 |
| Follow up | -.033 | .514** | -.266 | .107 | -.212 |

Note. Time Since Trauma = days since last primary trauma. PTSD symptoms = Child + Parent CPSS score at pretreatment.

* $p < .05$, two-tailed. ** $p < .01$, two-tailed.

Table 3

Correlations Between Heart Period (HP) Variables and Demographics

| HP Variable | Age | Gender | Race | Time Since Trauma | PTSD Symptoms |
|----------------|-------|--------|-------|-------------------|---------------|
| Resting HP | | | | | |
| Pretreatment | .140 | -.061 | .105 | .090 | -.071 |
| Post Treatment | -.039 | -.058 | -.081 | .079 | .153 |
| Follow up | .073 | -.330 | -.095 | -.081 | -.115 |
| HP Change | | | | | |
| Pretreatment | .094 | .183 | .269 | -.239 | -.011 |
| Post Treatment | -.018 | -.004 | .033 | -.108 | .026 |
| Follow up | .143 | -.102 | -.143 | .250 | -.379* |

Note. Time Since Trauma = days since last primary trauma. PTSD symptoms = Child + Parent CPSS score at pretreatment.

* $p < .05$, two-tailed.

Table 4

Gender Differences of Mean RSA Change Across Time for Low and High RSA groups

| Time | Low RSA | | | |
|----------------|--------------|-------------|----------------|-------------|
| | <u>Males</u> | | <u>Females</u> | |
| | <i>n</i> | M (SD) | <i>n</i> | M (SD) |
| Pretreatment | 10 | 0.10 (.24) | 6 | 0.19 (.33) |
| Post Treatment | 6 | -0.24 (.32) | 4 | 0.11 (.22) |
| Follow up | 6 | -0.35 (.29) | 4 | -0.08 (.14) |
| | High RSA | | | |
| | <i>n</i> | M (SD) | <i>n</i> | M (SD) |
| | | | | |
| Pretreatment | 11 | -0.34 (.24) | 5 | -0.29 (.37) |
| Post Treatment | 7 | -0.46 (.31) | 4 | -0.03 (.39) |
| Follow up | 5 | -0.28 (.51) | 3 | 0.02 (.02) |

Low and High RSA groups were created for the top and bottom 33% of pre-treatment resting RSA values. RSA = respiratory sinus arrhythmia.

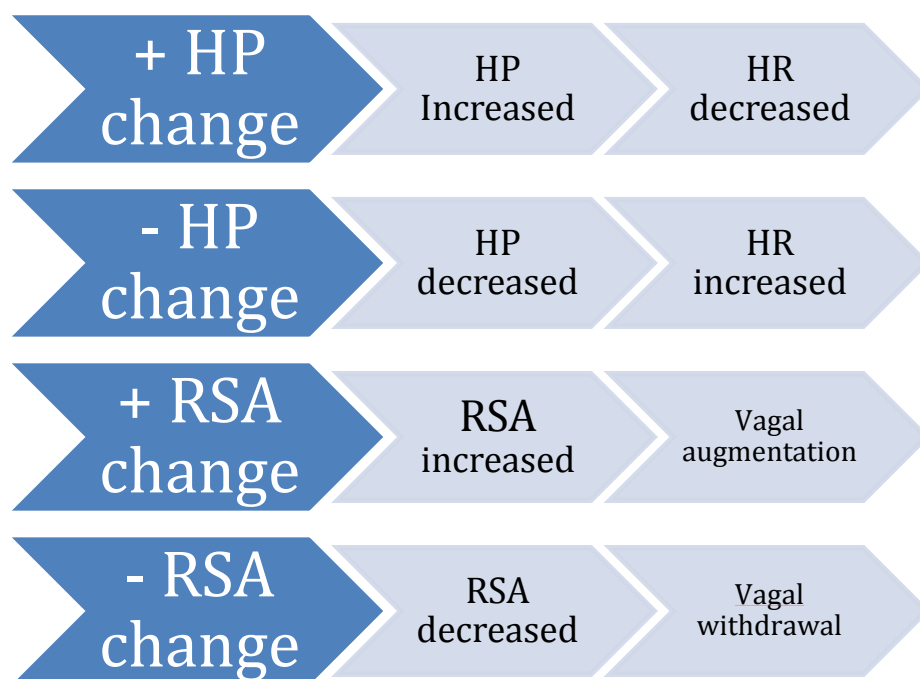


Figure 1. Directions of Heart Period (HP) and Respiratory Sinus Arrhythmia (RSA) Change scores. Change scores were calculated as mean values during script- resting.

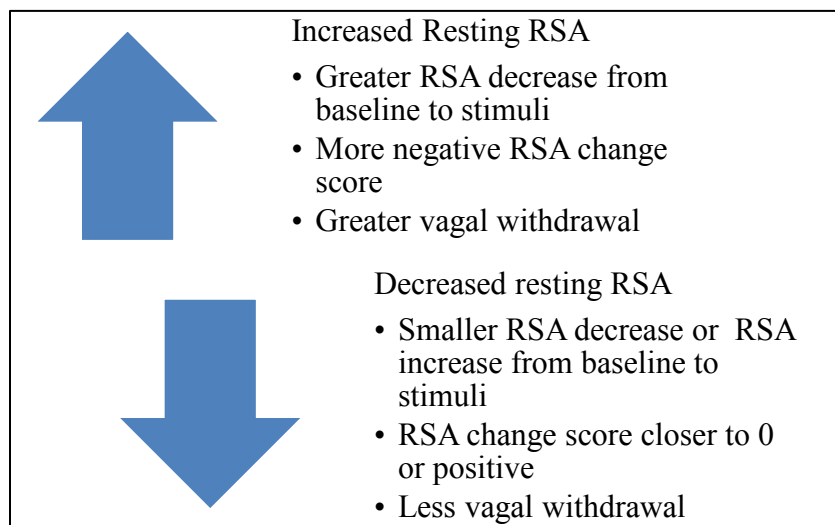


Figure 2. Directionality of Resting RSA and Reactivity. This figure illustrates the relationship between resting RSA and RSA reactivity. RSA= respiratory sinus arrhythmia. RSA change scores = mean RSA during trauma script- resting RSA.

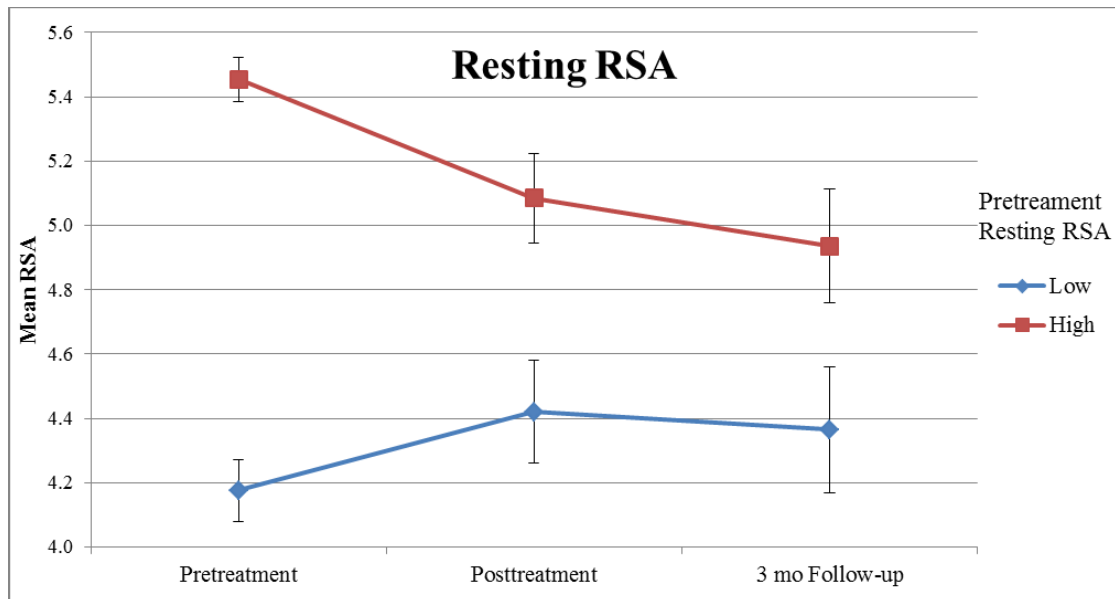


Figure 3. This figure illustrates the mean resting RSA values at all three time points. Low and High groups ($n=15$) were created for the top and bottom 33% of pre-treatment resting RSA values. At post treatment and follow up, Low group $n=10$, and High group $n=11$ and $n=8$ respectively. RSA= respiratory sinus arrhythmia. Error bars indicate standard error. Significant interaction between Pretreatment resting RSA \times Time $p = .001$

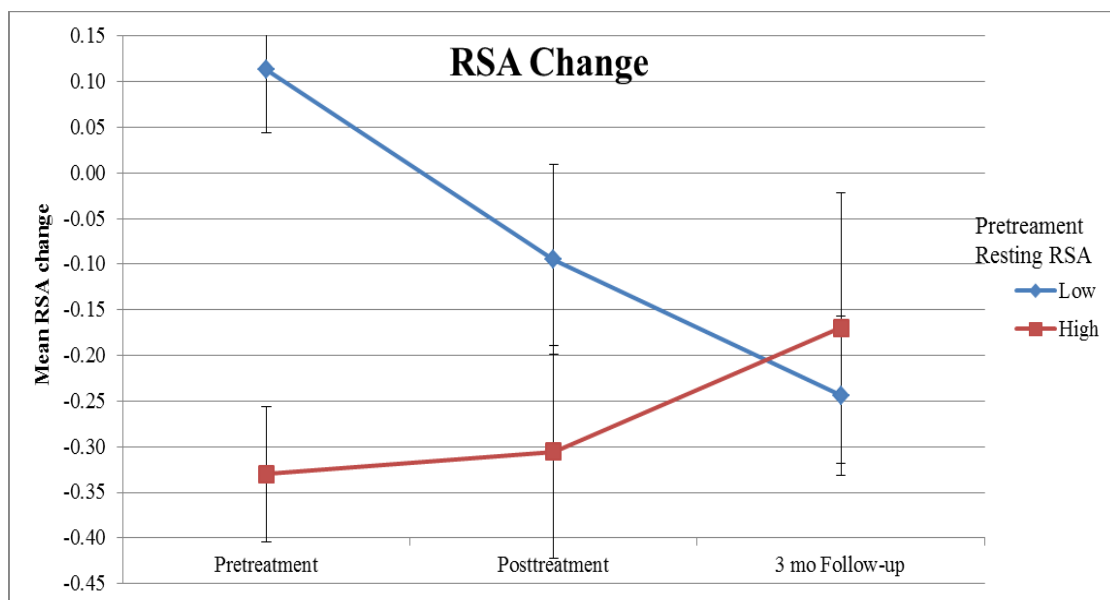


Figure 4. This figure illustrates mean RSA change scores for all three time points. RSA= Respiratory Sinus Arrhythmia. Change scores were calculated as RSA during script-resting RSA. Negative change scores indicate RSA or vagal withdrawal and positive change scores indicate RSA or vagal augmentation in response to trauma-related stimulus. Low and High groups ($n=15$) were created for the top and bottom 33% of pre-treatment resting RSA values. At post treatment and follow up, Low group $n=10$, and High group $n=11$ and $n=8$ respectively. Error bars indicate standard error. Significant interaction between Pretreatment resting RSA \times Time $p = .04$.

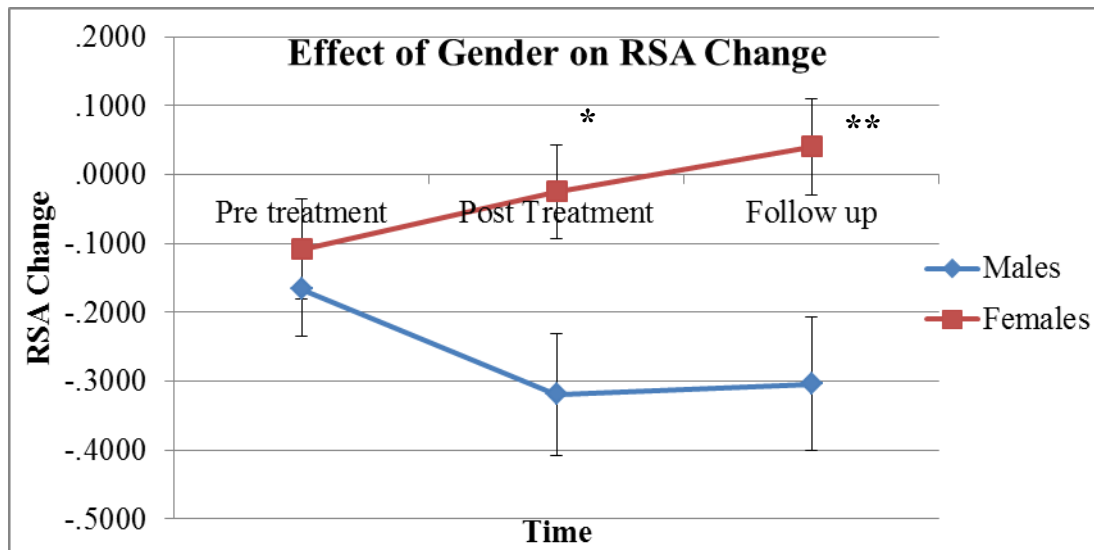


Figure 5. Gender differences on RSA change for all 3 time points For females, $n=20, 13, 13$, and for males $n= 28, 10, 10$, at pre-treatment, post-treatment and follow up respectively. RSA= Respiratory Sinus Arrhythmia. Change scores were calculated as RSA during script- resting RSA. Negative change scores indicate RSA or vagal withdrawal and positive change scores indicate RSA or vagal augmentation in response to trauma-related stimulus. Error bars indicate standard error. * $p<.05$, two-tailed. ** $p<.01$, two-tailed.

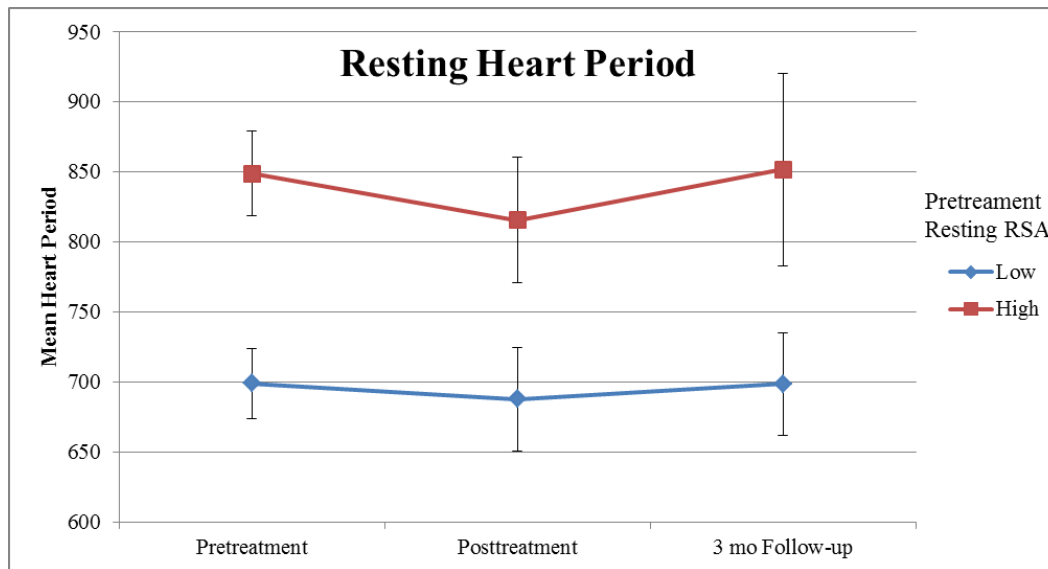


Figure 6. This figure illustrates mean resting Heart Period (HP) values across all three time points. Higher resting HP indicates lower resting heart rate. Low and High groups ($n=15$) were created for the top and bottom 33% of pre-treatment resting Respiratory Sinus Arrhythmia values. At post treatment and follow up, Low group $n=10$, and High group $n=11$ and $n=8$ respectively. Error bars indicate standard error. Significant effect of pretreatment resting RSA on resting HP, $p < .001$.

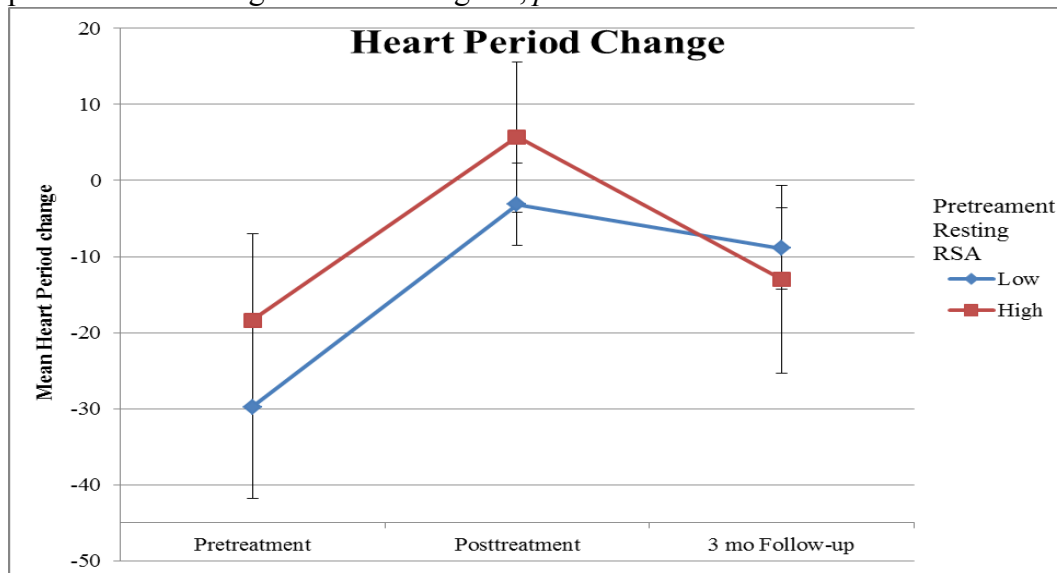


Figure 7. This figure illustrates Heart Period (HP) change scores across all three time points. Negative change scores indicate HP decreased (Heart rate increase) and positive change scores indicate HP increased (Heart rate decreased) in response to trauma-related stimulus. Low and High groups ($n=15$) were created for the top and bottom 33% of pre-treatment resting Respiratory Sinus Arrhythmia values. At post treatment and follow up, Low group $n=10$, and High group $n=11$ and $n=8$ respectively. Error bars indicate standard error. No significant effects observed.

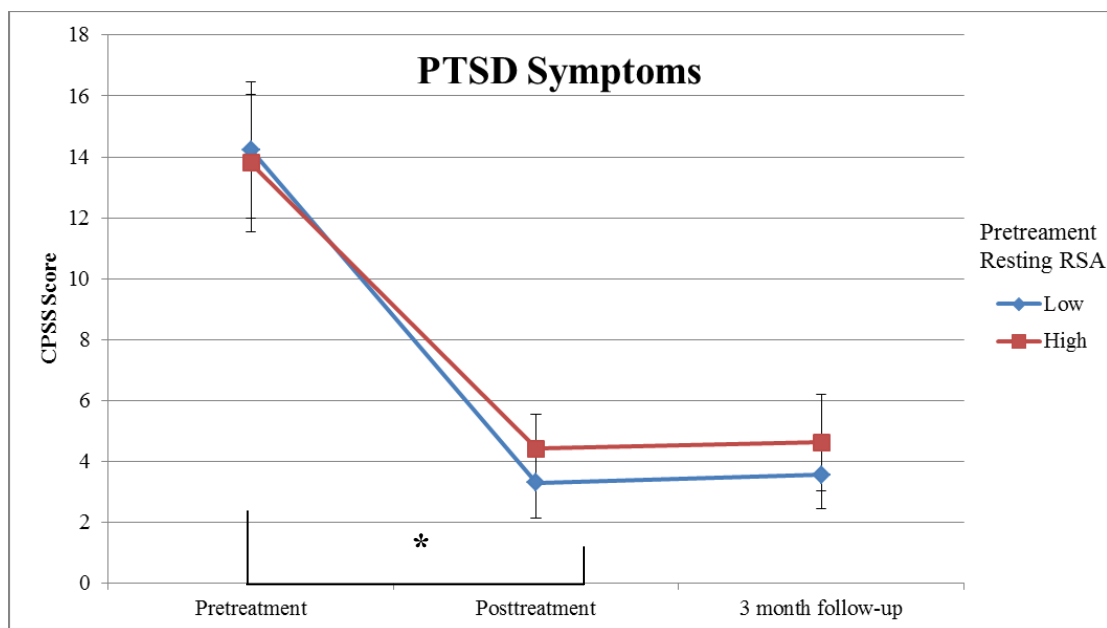


Figure 8. This figure compares mean CPSS scores at all three time points by High and Low RSA Groups. Low and High groups ($n=15$) were created for the top and bottom 33% of pre-treatment resting RSA values. At post treatment and follow up, Low group $n=10$, and High group $n=11$ and $n=8$ respectively. Error bars indicate standard error. RSA= Respiratory Sinus Arrhythmia, CPSS= Child PTSD Symptom Scale. CPSS Scores were measured as a joint Child + Parent score. $p < .0001$ for effect of time.

List of References

- Alkozei, A., Creswell, C., Cooper, P. J., & Allen, J. J. B. Autonomic arousal in childhood anxiety disorders: Associations with state anxiety and social anxiety disorder. *Journal of Affective Disorders*, (0) doi:<http://dx.doi.org/10.1016/j.jad.2014.11.056>
- American Psychiatric Association, APA, Asociación Americana de Psiquiatría, & A.P.A. (2013). *Diagnostic and statistical manual of mental disorders : DSM-5*. (Fifth ed.).
- Beckham, J., Taft, C., Vrana, S., Feldman, M., Barefoot, J., Moore, S., . . . Calhoun, P. (2003). Ambulatory monitoring and physical health report in vietnam veterans with and without chronic posttraumatic stress disorder. *Journal of Traumatic Stress*, 16(4), 329-335. doi:10.1023/A:1024457700599
- Blanchard, E. B. (1990). Elevated basal levels of cardiovascular responses in vietnam veterans with PTSD: A health problem in the making? *Journal of Anxiety Disorders*, 4(3), 233-237. doi:[http://dx.doi.org/10.1016/0887-6185\(90\)90015-2](http://dx.doi.org/10.1016/0887-6185(90)90015-2)
- Blanchard, E. B., Hickling, E. J., Veazey, C. H., Buckley, T. C., Freidenberg, B. M., Walsh, J. D., & Keefe, L. (2002). Treatment-related changes in cardiovascular reactivity to trauma cues in motor vehicle accident-related PTSD. *Behavior Therapy*, 33(3), 417-426. doi:10.1016/S0005-7894(02)80036-3
- Bornstein, M. H., & Suess, P. E. (2000). Physiological self-regulation and information processing in infancy: Cardiac vagal tone and habituation. *Child Development*, 71(2), 273-87.
- Boyce, W. T., & Ellis, B. J. (2005). Biological sensitivity to context: I. an evolutionary-developmental theory of the origins and functions of stress reactivity. *Development and Psychopathology*, 17(2), 271-301.
- Buckley, T. C., & Kaloupek, D. G. (2001). A meta-analytic examination of basal cardiovascular activity in posttraumatic stress disorder. *Psychosomatic Medicine*, 63(4), 585.
- Coan, J. A., Schaefer, H. S., & Davidson, R. J. (2006). Lending a hand: Social regulation of the neural response to threat. *Psychological Science (Wiley-Blackwell)*, 17(12), 1032-1039. doi:10.1111/j.1467-9280.2006.01832.x
- Cohen, Hagit Benjamin, Jonathan Geva, Amir B. Matar, Mike A. Kaplan, Zeev Kotler, Moshe. (2000). Autonomic dysregulation in panic disorder and in post-traumatic stress disorder: Application of power spectrum analysis of heart rate variability at rest and in response to recollection of trauma or panic attacks. *Psychiatry Research*, 96(1), 1-13. doi:10.1016/S0165-1781(00)00195-5
- Cohen, H., Kotler, M., Matar, M. A., Kaplan, Z., Miodownik, H., & Cassuto, Y. (1997). Power spectral analysis of heart rate variability in posttraumatic stress disorder patients. *Biological Psychiatry*, 41(5), 627-629. doi:10.1016/S0006-3223(96)00525-2
- Cohen, H., Kotler, M., Matar, M. A., Kaplan, Z., Loewenthal, U., Miodownik, H., & Cassuto, Y. (1998). Analysis of heart rate variability in posttraumatic stress disorder patients in response to a trauma-related reminder. *Biological Psychiatry*, 44(10), 1054-1059. doi:10.1016/S0006-3223(97)00475-7
- Cohen, H., Kotler, M., Matar, M. A., Kaplan, Z., Miodownik, H., & Cassuto, Y. (1997). *P.3.050 heart rate variability analysis in post-traumatic stress disorder patients in response to a trauma-related reminder* doi:10.1016/S0924-977X(97)88798-6

- Del Giudice, M., Ellis, B. J., & Shirlcliff, E. A. (2011). The adaptive calibration model of stress responsivity. *Neuroscience & Biobehavioral Reviews*, 35(7), 1562-1592. doi:<http://dx.doi.org/10.1016/j.neubiorev.2010.11.007>
- Friedman, B. H., & Thayer, J. F. (1998). Autonomic balance revisited: Panic anxiety and heart rate variability. *Journal of Psychosomatic Research*, 44(1), 133-151. doi:10.1016/S0022-3999(97)00202-X
- Garakani, A., Martinez, J. M., Aaronson, C. J., Voustianiouk, A., Kaufmann, H., & Gorman, J. M. (2009). Effect of medication and psychotherapy on heart rate variability in panic disorder. *Depression and Anxiety*, 26(3), 251-258. doi:10.1002/da.20533
- Grasso, D. J., & Simons, R. F. (2012). Electrophysiological responses to threat in youth with and without posttraumatic stress disorder. *Biological Psychology*, 90(1), 88-96. doi:<http://dx.doi.org/10.1016/j.biopsycho.2012.02.015>
- Graziano, P., & Derefinko, K. (2013). Cardiac vagal control and children's adaptive functioning: A meta-analysis. *Biological Psychology*, 94(1), 22-37. doi:10.1016/j.biopsycho.2013.04.011
- Grossman, P., Karemaker, J., & Wieling, W. (1991). Prediction of tonic parasympathetic cardiac control using respiratory sinus arrhythmia: The need for respiratory control. *Psychophysiology*, 28(2), 201-216. doi:10.1111/j.1469-8986.1991.tb00412.x
- Hauschildt, M., Peters, M. J. V., Moritz, S., & Jelinek, L. (2011). Heart rate variability in response to affective scenes in posttraumatic stress disorder. *Biological Psychology*, 88(2), 215-222. doi:10.1016/j.biopsycho.2011.08.004
- Hinnant, J. B., & El-Sheikh, M. (2013). Codevelopment of externalizing and internalizing symptoms in middle to late childhood: Sex, baseline respiratory sinus arrhythmia, and respiratory sinus arrhythmia reactivity as predictors. *Development and Psychopathology*, 25(02), 419-436.
- Hopper, J. W., Frewen, P. A., Sack, M., Lanius, R. A., & Van, d. K. (2007). The responses to script-driven imagery scale (RSDI): Assessment of state posttraumatic symptoms for psychobiological and treatment research. *Journal of Psychopathology and Behavioral Assessment*, 29(4), 249-268. doi:10.1007/s10862-007-9046-0
- Hopper, J. W., Spinazzola, J., Simpson, W. B., & van, d. K. (2006). Preliminary evidence of parasympathetic influence on basal heart rate in posttraumatic stress disorder. *Journal of Psychosomatic Research*, 60(1), 83-90. doi:10.1016/j.jpsychores.2005.06.002
- Kawachi, I., Sparrow, D., Vokonas, P. S., & Weiss, S. T. (1995). Decreased heart rate variability in men with phobic anxiety (data from the normative aging study). *The American Journal of Cardiology*, 75(14), 882-885. doi:10.1016/S0002-9149(99)80680-8
- Keane, T. M., Kolb, L. C., Kaloupek, D. G., Orr, S. P., Blanchard, E. B., Thomas, R. G., . . . Lavori, P. W. (1998). Utility of psychophysiological measurement in the diagnosis of posttraumatic stress disorder: Results from a department of veterans affairs cooperative study. *Journal of Consulting and Clinical Psychology*, 66(6), 914-923. doi:10.1037/0022-006X.66.6.914
- Kirsch, V., Wilhelm, F. H., & Goldbeck, L. (2011). Psychophysiological characteristics of PTSD in children and adolescents: A review of the literature. *Journal of Traumatic Stress*, 24(2), 146. doi:10.1002/jts.20620

- Kogan, A., Gruber, J., Shallcross, A. J., Ford, B. Q., & Mauss, I. B. (2013). Too much of a good thing? cardiac vagal tone's nonlinear relationship with well-being. *Emotion, 13*(4), 599-604. doi:10.1037/a0032725
- Lindauer, R. T. L., Meijel, v., E.P.M., Jalink, M., Olff, M., Carlier, I. V. E., & Gersons, B. P. R. (2006). Heart rate responsivity to script- driven imagery in posttraumatic stress disorder: Specificity of response and effects of psychotherapy. *Psychosomatic Medicine, 68*(1), 33-40.
- MacMillan, H. L., Georgiades, K., Duku, E. K., Shea, A., Steiner, M., Niec, A., . . . Schmidt, L. A. (2009). Cortisol response to stress in female youths exposed to childhood maltreatment: Results of the youth mood project. *Biological Psychiatry, 66*(1), 62-68. doi:10.1016/j.biopsych.2008.12.014
- Marcovitch, S., Leigh, J., Calkins, S. D., Leerks, E. M., O'Brien, M., & Blankson, A. N. (2010). Moderate vagal withdrawal in 3.5-year-old children is associated with optimal performance on executive function tasks. *Developmental Psychobiology, 52*(6), 603-608. doi:10.1002/dev.20462
- Mathewson, K. J., Schmidt, L. A., Miskovic, V., Santesso, D. L., Duku, E., McCabe, R. E., . . . Moscovitch, D. A. (2013). Does respiratory sinus arrhythmia (RSA) predict anxiety reduction during cognitive behavioral therapy (CBT) for social anxiety disorder (SAD)? *International Journal of Psychophysiology, 88*(2), 171-181. doi:<http://dx.doi.org/10.1016/j.ijpsycho.2013.03.016>
- McFall, M. E., Murburg, M. M., Ko, G. N., & Veith, R. C. (1990). Autonomic responses to stress in vietnam combat veterans with posttraumatic stress disorder. *Biological Psychiatry, 27*(10), 1165.
- McNally, R. J., Luedke, D. L., Besyner, J. K., Peterson, R. A., Bohm, K., & Lips, O. J. (1987). Sensitivity to stress-relevant stimuli in posttraumatic stress disorder. *Journal of Anxiety Disorders, 1*(2), 105-116. doi:10.1016/0887-6185(87)90001-6
- Mezzacappa, E., Kindlon, D., Earls, F., & Saul, j. P. (1994). The utility of spectral analytic techniques in the study of the autonomic regulation of beat-to- beat heart-rate- variability. *International Journal of Methods in Psychiatric Research, 4*(1), 29-44.
- Morales, S., Beekman, C., Bandon, A. Y., Stifter, C. A., & Buss, K. A. (2015). Longitudinal associations between temperament and socioemotional outcomes in young children: The moderating role of RSA and gender. *Developmental Psychobiology, 57*(1), 105-119. doi:10.1002/dev.21267
- Muraoka, M., Carlson, J., & Chemtob, C. (1998). Twenty- four- hour ambulatory blood pressure and heart rate monitoring in combat-related posttraumatic stress disorder. *Journal of Traumatic Stress, 11*(3), 473-484. doi:10.1023/A:1024400628342
- Obradovi, J., Bush, N. R., Stamperdahl, J., Adler, N. E., & Boyce, W. T. (2010). Biological sensitivity to context: The interactive effects of stress reactivity and family adversity on socioemotional behavior and school readiness. *Child Development, 81*(1), 270-289. doi:10.1111/j.1467-8624.2009.01394.x
- Orr SP, Metzger LJ, Lasko NB, et al. (2003). Physiologic responses to sudden, loud tones in monozygotic twins discordant for combat exposure: Association with posttraumatic stress disorder. *Archives of General Psychiatry, 60*(3), 283-288. doi:10.1001/archpsyc.60.3.283

- Orr, S. P., Metzger, L. J., Lasko, N. B., Macklin, M. L., Peri, T., & Pitman, R. K. (2000). De novo conditioning in trauma-exposed individuals with and without posttraumatic stress disorder. *Journal of Abnormal Psychology, 109*(2), 290-298.
- Orr, S. P., Lasko, N. B., Metzger, L. J., & Pitman, R. K. (1997). Physiologic responses to non-startling tones in vietnam veterans with post-traumatic stress disorder. *Psychiatry Research, 73*(1-2), 103-107. doi:[http://dx.doi.org/10.1016/S0165-1781\(97\)00110-8](http://dx.doi.org/10.1016/S0165-1781(97)00110-8)
- Orr, S., Meyerhoff, J., Edwards, J., & Pitman, R. (1998). Heart rate and blood pressure resting levels and responses to generic stressors in vietnam veterans with posttraumatic stress disorder. *Journal of Traumatic Stress; J.Trauma Stress, 11*(1), 155-164.
- Pallmeyer, T. P., Blanchard, E. B., & Kolb, L. C. (1986). The psychophysiology of combat-induced post-traumatic stress disorder in vietnam veterans. *Behaviour Research and Therapy, 24*(6), 645-652. doi:[http://dx.doi.org/10.1016/0005-7967\(86\)90059-8](http://dx.doi.org/10.1016/0005-7967(86)90059-8)
- Patriquin, M. A., Lorenzi, J., Scarpa, A., Calkins, S. D., & Bell, M. A. (2015). Broad implications for respiratory sinus arrhythmia development: Associations with childhood symptoms of psychopathology in a community sample. *Developmental Psychobiology, 57*(1), 120-130. doi:10.1002/dev.21269
- Pitman, R., Gilbertson, M., Gurvits, T., May, F., Lasko, N., Metzger, L., . . . Orr, S. (2006). Clarifying the origin of biological abnormalities in PTSD through the study of identical twins discordant for combat exposure. *Psychobiology of Posttraumatic Stress Disorder: A Decade of Progress; Ann.NY Acad.Sci., 1071*, 242-254. doi:10.1196/annals.1364.019
- Porges, S. W. (1995). Orienting in a defensive world: Mammalian modifications of our evolutionary heritage. A polyvagal theory. *Psychophysiology, 32*(4), 301-318. doi:10.1111/j.1469-8986.1995.tb01213.x
- Porges, S. W. (2003). Social engagement and attachment: A phylogenetic perspective. *Annals of the New York Academy of Sciences, 1008*, 31.
- Porges, S. W. (2007). The polyvagal perspective. *Biological Psychology, 74*(2), 116-143. doi:<http://dx.doi.org/10.1016/j.biopsycho.2006.06.009>
- Porges, S. W., Doussard-Roosevelt, J. A., Portales, A. L., & Greenspan, S. I. (1996). Infant regulation of the vagal "brake" predicts child behavior problems: A psychobiological model of social behavior. *Developmental Psychobiology, 29*(8), 697-712. doi:10.1002/(SICI)1098-2302(199612)29:8<697::AID-DEV5>3.0.CO;2-O
- Prins, A., Kaloupek, D., & Keane, T. (1995). In Prins A., Friedman M., Charney D. and Deutch A. (Eds.), *Psychophysiological evidence for autonomic arousal and startle in traumatized adult populations*
- Rasmusson, A. M., Hauger, R. L., Morgan III, C. A., Bremner, J. D., Charney, D. S., & Southwick, S. M. (2000). Low baseline and yohimbine-stimulated plasma neuropeptide Y (NPY) levels in combat-related PTSD. *Biological Psychiatry, 47*(6), 526-539. doi:[http://dx.doi.org/10.1016/S0006-3223\(99\)00185-7](http://dx.doi.org/10.1016/S0006-3223(99)00185-7)
- Sack, M., Hopper, J. W., & Lamprecht, F. (2004). Low respiratory sinus arrhythmia and prolonged psychophysiological arousal in posttraumatic stress disorder: Heart rate dynamics and individual differences in arousal regulation. *Biological Psychiatry, 55*(3), 284.

- Sack, M., Lempa, W., Steinmetz, A., Lamprecht, F., & Hofmann, A. (2008). Alterations in autonomic tone during trauma exposure using eye movement desensitization and reprocessing (EMDR)—Results of a preliminary investigation. *Journal of Anxiety Disorders*, 22(7), 1264-1271. doi:<http://dx.doi.org/10.1016/j.janxdis.2008.01.007>
- Sahar, T., Shalev, A. Y., & Porges, S. W. (2001). Vagal modulation of responses to mental challenge in posttraumatic stress disorder. *Biological Psychiatry*, 49(7), 637-643. doi:10.1016/S0006-3223(00)01045-3
- Saltzman, K., Holden, G., & Holahan, C. J. (2005). The psychobiology of children exposed to marital violence. *Journal of Clinical Child and Adolescent Psychology; J.Clin.Child Adolesc.Psychol.*, 34(1), 129-139.
- Shaffer D, Fisher P, Lucas C: NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): Description, differences from previous versions, and reliability of some common diagnoses. *J Am Acad Child Adolesc Psychiatry* 39, 28–38, 2000.
- Scheeringa, M. S., Zeanah, C. H., Myers, L., & Putnam, F. (2004). Heart period and variability findings in preschool children with posttraumatic stress symptoms. *Biological Psychiatry*, 55(7), 685-691. doi:10.1016/j.biopsych.2004.01.006
- Stifter, C., & Fox, N. (1990). Infant reactivity - physiological correlates of newborn and 5-month temperament. *Developmental Psychology; Dev.Psychol.*, 26(4), 582-588.
- Yeragani, V. K., Pohl, R., Berger, R., Balon, R., Ramesh, C., Glitz, D., . . . Weinberg, P. (1993). Decreased heart rate variability in panic disorder patients: A study of power-spectral analysis of heart rate. *Psychiatry Research*, 46(1), 89-103. doi:10.1016/0165-1781(93)90011-5
- Zoladz, P. R., & Diamond, D. M. (2013). Current status on behavioral and biological markers of PTSD: A search for clarity in a conflicting literature. *Neuroscience & Biobehavioral Reviews*, 37(5), 860-895. doi:<http://dx.doi.org/10.1016/j.neubiorev.2013.03.024>

Biography

Rebecca Sara Lipschutz was born on April 15, 1992 in New Brunswick, New Jersey. She graduated from Princeton High School in New Jersey and then continued her education at Tulane University in New Orleans, Louisiana. Rebecca graduated from Tulane University cum laude in 2014 with a Bachelor of Science in Neuroscience. She will graduate from Tulane University in 2014 with her Master of Science in Neuroscience. After her Master's degree, Rebecca plans to pursue her Ph.D.