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Respiratory Sinus Arrhythmia in Cognitive Behavioral Therapy for Posttraumatic Stress Symptoms in Children: Preliminary Treatment and Gender Effects

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Abstract

Cognitive behavioral therapy (CBT) is an efficacious treatment for posttraumatic stress disorder (PTSD) symptoms, but the effect of CBT on physiological indicators is largely unknown. Respiratory sinus arrhythmia (RSA) is an established parasympathetic marker of self-regulatory capacity and stress responsivity. The present study tested if and how resting RSA and RSA reactivity changed following treatment among a sample of children ($n=48$) who experienced at least one traumatic event and presented with PTSD symptoms. RSA reactivity was measured in response to personalized trauma-related scripts. Results indicated that changes in RSA after treatment were dependent on pretreatment resting levels of RSA, with individuals with high and low pretreatment resting RSA levels appearing to converge over time in both resting RSA and RSA reactivity by the 3-month follow up. Specific to RSA reactivity, a sex difference was evident, as following treatment, females showed less RSA withdrawal whereas males showed more RSA withdrawal. PTSD symptoms were significantly reduced after CBT but symptom change was not associated with pretreatment resting RSA levels. Overall, these results suggest that there may be multiple physiological patterns within children with PTSD and the direction of the physiological changes after CBT may depend on initial differences in resting RSA levels.

Keywords

Psychotherapy; Post-traumatic stress; Respiratory sinus arrhythmia; Youth

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Introduction

There is substantial evidence indicating that cognitive behavioral therapy (CBT) improves posttraumatic stress disorder (PTSD) symptoms in children and adolescents (see review, Miller-Graff and Champion 2016), but it is largely unknown if or how physiological indicators of stress response systems change in response to treatment, or how they may relate to treatment response. Research has shown physiological differences in the stress response systems in individuals with PTSD compared to individuals without PTSD (Zoladz and Diamond 2013) such as increased autonomic arousal (i.e., exaggerated startle and hypervigilance) and heightened reactivity to trauma reminders. Thus, disentangling if CBT is able to affect change in individuals with PTSD at both the symptom and physiological level is important for understanding psychotherapy mechanisms and effectiveness. In a recent review of adult studies related to physiological response to PTSD treatment, it was concluded that it is ambiguous as to whether neurobiology changes with treatment (Zantvoord et al. 2013; Barsaglini et al. 2014).

Physiological indices may offer objective measures of affective and self-regulatory responses that could provide additional insight to complement self-report of symptoms. One such psychophysiological indicator that holds promise as a marker of self-regulatory capacity and emotion regulation is respiratory sinus arrhythmia (RSA) (Beauchaine 2001; Beauchaine et al. 2007; Porges 2007). As a critical goal of psychotherapy for PTSD is to help individuals learn to regulate negative emotions such as anxiety or increased arousal when exposed to trauma related reminders, measuring changes in RSA with treatment may indicate improved abilities to regulate emotions or decreased arousal in an objective, physiological measure. RSA is a reliable index of parasympathetic stress reactivity and measures high-frequency heart period variability (HF-HPV). RSA is commonly used to measure phasic, vagal cardiac control and accounts for much of the variability observed in heart rate (Berntson and Cacioppo 2007; Grossman and Taylor 2007; Porges 1995). 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 min. 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. The capacity to spontaneously disengage and re-engage the “vagal brake” is indicated by higher resting RSA or greater RSA reactivity to challenges.

The empirical literature indicates *higher resting RSA* (i.e., more variability) is associated with greater abilities to regulate stress, emotional arousal, and attention (e.g., Bornstein and Suess 2000; Porges et al. 1996; Stifter and Fox 1990). *Lower resting RSA* has been implicated with the greater psychophysiological arousal observed in chronic stress activation and anxiety disorders (Friedman and Thayer 1998; Kawachi et al. 1995; Yeragani et al. 1993). Theoretically, resting RSA may increase following interventions such as CBT or possibly predict treatment outcome. That is higher resting RSA may be associated with better treatment outcomes.

Individual differences in regulating this vagal brake can also be measured by *RSA reactivity* to stressful stimuli (Graziano and Derefinko 2013). Porges (2007) has proposed that RSA withdrawal (disengaging the vagal brake or RSA decrease from resting to stressor) during times of stress 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 RSA withdrawal or an increase in RSA (RSA augmentation) in response to stressful contexts may indicate a maladaptive response associated with poor outcomes. However, there is also evidence that excessive RSA withdrawal in response to emotion evocation tasks is associated with increased internalizing and externalizing symptoms in children (Beauchaine 2015). These RSA patterns may change following interventions such as CBT. However, as there is limited research in this area, it is not known if RSA reactivity changes as a result of treatment or predicts treatment effects, but both questions may have important clinical implications.

RSA and PTSD

In terms of resting RSA, a number of studies in adults have shown that individuals with PTSD display lower levels of resting RSA compared to healthy controls and trauma exposed individuals without PTSD (Cohen et al. 1998; Sack et al. 2004; Jovanovic et al. 2009; Hauschildt et al. 2011). In terms of RSA reactivity to a stressor, studies have shown both blunted reactivity and increased reactivity in individuals with PTSD (Cohen et al. 1998; Hauschildt et al. 2011; Sack et al. 2004). Compared to the substantial literature on adult PTSD, there are relatively fewer studies on psychophysiology in pediatric PTSD samples. Scheeringa et al. (2004) found altered RSA reactivity to a trauma script in trauma-exposed children regardless of PTSD diagnosis compared to non-trauma exposed controls. Kirsch et al. (2015) did not find differences in sympathetic or parasympathetic measures, including RSA, at rest or in response to a trauma-related script between groups with and without PTSD. Within individuals with PTSD, the findings on RSA reactivity to stressful stimuli are inconsistent, and there is limited evidence about changes in RSA associated with treatment.

Physiological Changes Associated with PTSD Treatment

In regards to *physiological changes associated with treatment* for PTSD in adult samples, the findings have been conflicting. Sack et al. (2008), found increased heart rate variability (HRV) after eye movement desensitization and reprocessing treatment among adults, and Garakani et al. (2009) also found increased HRV after CBT in adults diagnosed with PTSD and panic disorder. Hinton et al. (2009), finding that CBT was followed by increased emotion regulation and changes in systolic blood pressure regulation in Cambodian refugees, speculated that decreased vagal tone played a role in the generation of PTSD. 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 that psychotherapy did not appear to influence acoustic startle reflex, heart rate response, or skin conductance. While the treatment findings are mixed, theoretically resting RSA and RSA reactivity are promising constructs to examine as indices of physiological responses to CBT.

The Present Study

Theory and empirical evidence suggest lower resting RSA and either blunted or excessive RSA reactivity in response to trauma-related stimuli in adults are associated with PTSD. As the majority of literature is limited to adult participants, less is known about how these RSA patterns may translate to pediatric populations. This study goes beyond previous studies by examining RSA patterns in children with PTSD symptoms and how they change after treatment. Understanding if and how RSA patterns change with treatment is an important next step in understanding RSA in youth. Theoretically, treatment should increase emotion regulation and therefore increase resting RSA. However, youths initial resting RSA may affect which direction changes occur. That is, it may not be simply that higher resting RSA is better but that there is an optimal level of resting RSA. We used data from a randomized trial of CBT to treat PTSD in children (Scheeringa and Weems 2014) to examine whether pretreatment resting RSA predicts trajectories of resting RSA and RSA reactivity (measured as RSA withdrawal during trauma-related script-driven imagery) after psychotherapy treatment. Pretreatment resting RSA was chosen as a predictor to examine the idea that it is not simply that higher resting RSA is better (or increases after treatment) but that there is an optimal level of resting RSA. That is, treatment may attune RSA back to an individual's optimal level as opposed to just increasing resting levels. Moreover, pretreatment resting RSA may prove to be a relatively uncomplicated neurobiological metric to obtain which can predict treatment response. Thus analyses were also conducted to test if pretreatment RSA predicted differential symptom change. Due to the potential sex differences (Morales et al. 2015; Gray et al. 2016; Hinnant and El-Sheikh 2013), variation by child sex was also explored as a covariate.

Method

Participants

Participants for this study were drawn from a randomized trial examining the effects of D-cycloserine (DCS) and CBT on children with PTSD (Scheeringa and Weems 2014). 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; most exclusions were due to not presenting with enough PTSD symptoms to reach the study threshold. Forty-eight of the participants had valid and usable physiological data and demographics are presented in Table 1. The three subjects without physiological data were due to technical issues with data collection.

Participants for this study include 48 children, 7–13 years old ($M = 9.7$, $SD = 1.9$), who experienced at least one potentially traumatic event and presented with five or more PTSD symptoms plus functional impairment. Exclusion criteria included a Glasgow Coma Scale score of five or less in the emergency room; intellectual disability (ID) as indicated by standard scores below 50 on the Peabody Picture Vocabulary Test, a measure of receptive vocabulary was used in this study as a cost effective estimate of moderate ID; autistic disorder, from clinical observations by the principal investigator; blindness; deafness; non-English speaking family; suicidal, homicidal, or gravely disabled; receiving concurrent counseling outside of the study; any kidney or liver ailment; epilepsy or history of seizures;

and history of diagnosis of bipolar disorder or schizophrenia. Psychoactive medications were allowed as long as the dose had been stable at least 4 weeks prior to treatment and remained stable. Participants were assessed for psychological symptoms and physiological measures at pretreatment, posttreatment and a 3-month follow up. Treatment included completion of 12 weeks of cognitive behavioral therapy (CBT).

Procedure

The Tulane University Committee on the Use of Human Subjects approved this study. When participants arrived at the laboratory, the study was explained to the caregivers and youth orally and in writing. Written informed consent was obtained from the caregivers. Written assent was obtained from the youth.

Measures

Diagnostic Interview Schedule for Children-IV—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 et al. 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.

Child PTSD Symptom Scale—The Child PTSD Symptom Scale (CPSS) was used to show change in PTSD severity over time as change in symptom severity may have more clinical significance than change in diagnosis. The CPSS is a self-administered measure of the 17 PTSD DSM-IV symptoms rated on a 4-point (0–3) Likert scale (Foa et al. 2001). This yields a broader range of scores that indicate intensity and frequency that may be more sensitive to change than the number of PTSD symptoms. This measure was administered pretreatment, posttreatment and at 3-month follow-up. Child and parent versions were used and a joint score was created using an either/or rule.

Physiological Data Collection

RSA was 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 resting 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. Data were collected with equipment and software from the James Long Company (Cargoga Lake, New York). The bioamplifier was set for bandpass filtering at frequencies of 0.1 and 1000 Hz. Data were digitized at a sampling rate of 512 Hz with a 12-bit A–D board in a laboratory computer. Electrocardiogram was resampled off-line at 1000 Hz. The rising edges of the R waves were automatically identified with a multiple-pass, self-scaling algorithm. An interactive graphic program enabled visual inspection for manual correction of missed or misidentified R waves. RSA reflects high frequency HRV and was estimated from power

spectral analysis in the empirically validated respiratory frequency for the child's age (Scheeringa et al. 2004). Frequency bands of 0.2–0.65 Hz were used for the children in this study. This frequency band was the most similar to the 0.24–1.04 Hz common to child studies of HRV and RSA (Hickey et al. 1995; Suess et al. 1997; Porges et al. 2007).

Mean RSA values were calculated for 1-min resting baseline and trauma script epochs and natural log transformed. To measure RSA reactivity in response to trauma stimuli, RSA reactivity scores were calculated by subtracting the mean RSA for the preceding 1-min resting baseline from the mean RSA for the 1 min trauma script stimuli. *Negative RSA reactivity score* indicates that RSA decreased (vagal withdrawal, or relatively less application of the vagal brake) in response to the stimulus. A *positive RSA reactivity 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 CBT 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 two authors (MS and CW). For additional details on YPT its components please see (Scheeringa and Weems 2014).

Data Analysis

The trajectories of resting RSA and RSA reactivity were tested with repeated measures mixed model analyses using the PROC MIXED statement in SAS 9.3 (Cary, NC). Mixed models handles missing data without excluding participants using likelihood based estimation method. Thus, despite dropout (described below), analyses included all 48 participants across time. RSA values were natural log transformed. A simple model (Model 1) with time, pretreatment resting RSA and pretreatment resting RSA $\times$ time was first tested to examine which covariance structure was the best fit. The outcome variables were resting RSA and RSA reactivity at posttreatment and follow up.

All RSA predictor and outcome variables for all hypotheses were tested for association with potential covariates age, sex, race, PTSD symptoms, number of traumas, and time since trauma as shown in Table 2. As the participants were taken from a DCS study, drug status (DCS or placebo) was also tested for association with RSA outcome variables and no significant correlations were found, consistent with the main finding of the parent study that DCS did not affect PTSD outcomes (Scheeringa and Weems 2014). We also tested associations between children on any medication (med) and specifically medication that impacts cardiovascular functioning (cmed; clonidine, guanfacine, and stimulant medications) with outcome variables. Only variables that showed significant bivariate correlations with outcome variables were included as covariates in further mixed model tests. Variables with no significant correlations to outcome variables were not included in the

mixed models as covariates. Covariates were added to the simple model and if significant were further tested for interactions. A stepwise model building approach was used and AIC and BIC was used to compare model fit.

Results

Preliminary Analysis

To choose the best covariance structures, the same simple model was tested with both unstructured and autoregressive structures. Due to the correlations between RSA reactivity at pretreatment and posttreatment, and because smaller AIC and BIC values indicated improved fit, autoregressive was chosen as the covariance structure for all tests.

Out of the 48 children who had physiological data at pretreatment, there were 17 children who dropped out by post-treatment and 3 additional children who dropped out by follow up. Treatment non-completers did not differ from completers based on age, race, sex, total number of traumas (child and parent report), severity of PTSD symptoms (joint report) at pretreatment, resting RSA, or RSA reactivity. Treatment non-completers had significantly younger mothers (mean = 35.6, SD = 1.9 vs. mean = 45.8, SD = 12.7), mothers with fewer years of education (mean = 12.3, SD = 2.0 vs. mean = 14.9, SD = 3.1), younger fathers (mean = 34.6, SD = 4.5 vs. mean = 42.9, SD = 9.0), and had fathers with fewer years of education (mean = 10.9, SD = 2.4 vs. mean = 12.8, SD = 2.2), compared to completers; all Wilcoxon Rank Sum p s < .05. The mean duration from the last trauma to the time of assessment was 808.4 days (SD = 742.7). We note additionally that time since last trauma was not correlated with any outcomes.

The only significant bivariate correlation found between outcome RSA variables and potential covariates (see Table 2) was between sex and RSA reactivity scores at posttreatment and follow up, ($r = .44$, $p < .05$ and $r = .52$, $p < .01$), with males demonstrating more negative RSA reactivity than girls, so sex was included as a covariate in subsequent analyses. There was also a significant bivariate correlation between pretreatment resting RSA and pre-treatment RSA reactivity ($r = -.43$, $p < .01$). Higher pre-treatment resting RSA was correlated with more negative RSA reactivity scores (suppression of vagal brake during stressful stimuli, or greater vagal withdrawal) in response to the trauma script.

Trajectories of Resting RSA and RSA Reactivity After CBT

Resting RSA—In Model 1 for the trajectory of resting RSA, there was a significant main effect of time (estimate = 1.15, $t(55) = 3.59$, $p < .001$), and a significant main effect of pretreatment resting RSA (estimate = 1.21, $t(46) = 9.05$, $p < .001$). However these main effects must be considered in light of significant interaction between time and pretreatment resting RSA (estimate = -0.26 , $t(55) = -3.89$, $p < .001$), suggesting that resting RSA changed differentially over time with respect to participants' resting RSA levels at pretreatment. To visually decompose the interaction, high and low groups were created from the top and bottom 33% of resting RSA values in the sample at pretreatment and graphed as depicted in Fig. 1. Although it is more conventional to use ± 1 SD to compare across groups, due to the small sample size, we chose to use top and bottom 33% so more

participants were included ($n = 16$ for both groups at pretreatment). As illustrated in Fig. 1, children in the High Resting RSA group at pretreatment showed a decrease in resting RSA across posttreatment and follow up, whereas children who started in the Low Resting RSA group at pretreatment showed an increase in resting RSA across posttreatment and follow up.

In Model 2, sex was added as a potential moderator. As shown in Table 3, adding sex did not yield any new significant effects or interactions, and time, pretreatment resting RSA, and time $\times$ pretreatment resting RSA were still significant. Thus, we considered Model 1 to be our best fit in predicting the trajectory of resting RSA over time.

RSA Reactivity—In Model 1 for predicting the trajectory of RSA reactivity, there was a significant main effect of time (estimate = -0.75 , $t(55) = -2.42$, $p = .02$), as well as a main effect of pretreatment resting RSA (estimate = -0.41 , $t(46) = -3.11$, $p = .03$). Additionally, a significant interaction between pretreatment resting RSA and time was observed (estimate = 0.16 , $t(55) = 2.42$, $p = .02$), suggesting that, like resting RSA, RSA reactivity also changed differentially over time with respect to varying levels of pretreatment resting RSA.

Again, visual inspection of graphs of children at the top and bottom 33% of pretreatment RSA resting values was used to decompose the interaction. Figure 2 illustrates trajectories of RSA reactivity over time for children who began with higher pretreatment resting RSA and lower pre-treatment resting RSA. Children with higher pretreatment resting RSA showed relatively more negative RSA reactivity at pretreatment (more vagal withdrawal, mean RSA reactivity score at pretreatment for high group = -0.33), whereas children with lower pretreatment resting RSA did not exhibit RSA withdrawal at pretreatment (showed vagal augmentation, mean RSA reactivity score of low group = 0.13), evidenced by either a blunted response (RSA reactivity score close to 0) or an increase in RSA (positive RSA reactivity score). Figure 2 additionally shows the trajectory of RSA reactivity from pretreatment to posttreatment and 3-month follow-up. Children with higher pretreatment resting RSA changed over time from relatively more negative RSA reactivity (greater vagal withdrawal) to relatively less negative RSA reactivity (relatively less vagal withdrawal). In contrast, those with lower pretreatment resting RSA changed in the opposite direction, moving from positive RSA reactivity score (either blunted response or vagal augmentation) to more negative RSA reactivity scores (relatively more vagal withdrawal). By follow up, children with higher pretreatment resting RSA showed similar RSA reactivity (mean RSA reactivity score at follow up of high group = -0.17) to children with lower pretreatment resting RSA (mean RSA reactivity score at follow up of low group = -0.24).

Sex was added to Model 2 to explore potential moderation of the RSA reactivity trajectory. There were significant main effects of time (estimate = -0.86 , $t(54) = -2.88$, $p = .01$) and pretreatment resting RSA (estimate = -0.038 , $t(43) = -2.97$, $p = .01$). In addition to the pretreatment resting RSA by time interaction described above (estimate = 0.16 , $t(54) = 2.64$, $p = .01$), there was additionally a significant sex by time interaction (estimate = 0.17 , $t(54) = 2.28$, $p = .03$). As shown in Fig. 3, males and females showed similar RSA reactivity at pretreatment, but changed differentially over time. After treatment, males showed more negative RSA reactivity (more vagal withdrawal) whereas females showed blunted RSA

reactivity or positive RSA reactivity (vagal augmentation). The main effect of sex was nonsignificant (estimate = 0.13, $t(43) = 0.22$, $p = .83$), and the interaction between sex and pretreatment resting RSA was also nonsignificant (estimate = -0.05, $t(43) = -0.38$, $p = .70$). Cmed was included as covariate (estimate = 0.15, $t(43) = 2.07$, $p = .04$). As shown in Model 3 in Table 3, the three-way resting RSA $\times$ time $\times$ sex interaction was not significant, suggesting that despite sex differences in RSA reactivity over time, pretreatment resting RSA levels do not differentially impact RSA reactivity patterns across treatment for males and females. In Model 4, all nonsignificant interaction terms were removed; see Table 3 for the final model.

Predicting PTSD Symptom Change

To test the idea that RSA predicts symptoms outcomes a similar mixed model was used to assess if PTSD symptoms changed after CBT and if pretreatment resting RSA predicted change in PTSD symptoms. There was a significant main effect for time ($F(1, 46) = 74.93$, $p < .0001$), indicating that PTSD symptoms were significantly reduced after CBT. There was no main effect of pretreatment resting RSA ($F(1, 46) = 0.93$, $p < .34$). When an interaction term of pretreatment resting RSA and time was added to the model, the interaction was not significant ($F(1, 46) = 0.53$, $p = .47$), suggesting that PTSD symptom reduction over time was not associated with pretreatment resting RSA. Figure 4 illustrates that those with high and low pretreatment resting RSA showed similar levels of PTSD symptomatology at pretreatment as well as similar symptom reductions after CBT.

Discussion

This study makes several contributions to our understanding of how physiological indicators of stress response systems change in response to treatment. First, the main research question was to examine how resting RSA and RSA reactivity change after CBT and if changes across treatment were predicted by pretreatment resting RSA. 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. As there are limited and contradictory findings in previous studies on the direction resting RSA changes after treatment, our results help explain why there may be inconsistent findings. Previous studies in adults have shown both increased resting RSA after treatment (Sack et al. 2008; Garakani et al. 2009), decreased resting RSA after treatment (Mathewson et al. 2013), and in children, no change in physiology after treatment (Grasso and Simmons 2012). However, unlike this report, these studies did not account for pretreatment resting RSA levels or examine if there were more than one direction of change.

Our findings are somewhat inconsistent with the idea that resting RSA is linearly associated with positive outcomes, (i.e., higher resting RSA is better) and that individuals with PTSD exhibit lower levels of RSA (Cohen et al. 1998; Sack et al. 2004; Jovanovic et al. 2009; Hauschildt et al. 2011). Our results showed different trajectories of change over time dependent on individual differences in resting RSA, suggesting more than one pattern of physiological change across treatment. Specifically, two patterns emerged. Among children who began with lower resting RSA, their resting RSA increased over time, and among

children who began with higher resting RSA, their resting RSA decreased over time. Given that neither resting patterns nor patterns of change were associated with changes in PTSD symptoms, and that both patterns changed across treatment, it seems imprudent to conclude that one pattern is more adaptive than the other.

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

RSA Reactivity

In addition to differential patterns of resting RSA over time, children's RSA reactivity across treatment varied in relation to their pretreatment resting RSA levels. Over time, and ostensibly due to treatment, those with higher pretreatment resting RSA decreased the magnitude of RSA reactivity when presented with a trauma-related stimulus by moving from relatively more negative RSA reactivity scores to relatively less negative RSA reactivity scores (i.e., less RSA withdrawal over time). Conversely, those with lower pretreatment resting RSA increased their negative RSA reactivity (more RSA withdrawal) over time by moving from positive RSA reactivity scores to negative RSA reactivity scores (i.e., application of the vagal brake to withdrawal of the vagal brake in response to stimulus). RSA reactivity also appeared to converge around moderate RSA withdrawal for children with both high and low pretreatment resting RSA. Most previous speculations have considered RSA withdrawal (negative RSA reactivity) as the more adaptive physiological response to stress, but those have been limited mostly to cross-sectional studies and there is also evidence that excessive RSA withdrawal is associated with symptoms of both internalizing and externalizing psychopathology (Beauchaine 2015), which are both highly comorbid with PTSD (Saigh et al. 2002). Comorbid internalizing and externalizing symptoms predict greater RSA withdrawal to emotion evocation tasks than either internalizing or externalizing alone (Calkins et al. 2007; Pang and Beauchaine 2013).

Since both high and low RSA patterns changed after treatment and there was no between-group difference on PTSD symptom improvement, it is difficult to infer if either RSA pattern is "better" or more adaptive at pretreatment. This provides evidence that is consistent with the biological sensitivity to context theory (BSC) (Boyce and Ellis 2005) or the adaptive calibration model (ACM) (Del Giudice et al. 2011) 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 in a PTSD/traumatic stress population. Due to the nature of our sample, we cannot determine what would be high or low RSA reactivity compared to a non PTSD or non-traumatized sample, but this suggests that within PTSD samples, there is variability in resting RSA and RSA reactivity, as well as in change over time across treatment. Our findings of both high and low levels of RSA reactivity at pretreatment are consistent with the theory suggested in ACM that severe or traumatic stress can develop into stress response

patterns of either high or low physiologic reactivity and there may be sex-typical patterns of reactivity, as described in the next section.

While it is difficult to speculate from these data whether one particular pattern is more adaptive at pretreatment, the convergence of the two groups across time into a mid-range of resting RSA and RSA reactivity by follow up, presumably in response to treatment, is consistent with prior work that has suggested that moderate levels of resting RSA and RSA reactivity may be optimal and associated with optimal performance (Hinnant and El-Sheikh 2009, 2013). For example, Marcovitch et al. (2010) found that children with moderate decreases in RSA outperformed children whose RSA decreased by too much or too little during executive functioning tasks. It may be that children who fail to show RSA withdrawal have difficulty reacting to environmental stressors, whereas children with extremely high RSA withdrawal are physiologically over-aroused, and that the convergence towards mid-range across these groups over treatment is reflective of a more optimal arousal.

Sex Differences

To further complicate the individual variability observed in RSA findings, our data suggests there may be sex differences that moderate RSA reactivity in children. In this study, males showed greater RSA withdrawal after treatment, and females showed lower RSA withdrawal and even RSA augmentation in response to the trauma-related stimulus. It may be that higher RSA reactivity may be more adaptive for males whereas lower RSA reactivity may be more adaptive for females. This is consistent with the limited literature on youth sex differences in RSA reactivity and psychopathology and extends the current literature into a PTSD population. Similarly, Morales et al. (2015) and Hinnant and El-Sheikh (2013) found that females with low RSA reactivity (less RSA withdrawal) and males with higher RSA reactivity (more RSA withdrawal) displayed less externalizing or internalizing symptoms. Our finding also builds upon Gray et al. (2016), which found that females with high exposure to potentially traumatic events, low RSA reactivity was more adaptive, evidenced by lower internalizing symptoms. Hinnant and El-Sheikh (2013) suggested that for females, showing high RSA reactivity may indicate overarousal and dysregulation towards stressors in certain contexts. A potential cause for these sex differences could include differences in how males and females interpret and cope with stressful situations (Morales et al. 2015). Taking these findings with our results suggests that different patterns of RSA reactivity may be more adaptive for females versus males in how they learn to respond to and cope with stress and regulate their emotions.

Our sample did not include a control group, such as trauma-exposed without PTSD symptoms, non-trauma exposed, or a control arm who was not receiving PTSD treatment. 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; however, there is evidence for resting RSA to be relatively stable over time in children (Doussard-Roosevelt et al. 2003). This study also had a small sample size and includes children in a 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 allowed a practice effect since the children knew what to expect at the later time points. Some children may have been anxious to repeat the testing, while others may have habituated to the testing procedures. Additionally, our measurement of 1-min baseline was shorter than some of existing literature examining RSA in children but is still considered valid (Quintana et al. 2016).

Conclusions

This study is one of few studies to examine physiological changes after treatment in children with PTSD and found changes in both PTSD symptoms and RSA indices after CBT. It was somewhat surprising that there was no association with PTSD symptoms. This is also the first known study to show how RSA indices can change differentially after CBT based on resting RSA at pretreatment and suggests that there may be optimal ranges of resting RSA and RSA reactivity. Taken with other existing studies, it questions the generalizability of maladaptive physiological patterns observed and suggests multiple physiological patterns within PTSD pediatric populations which should be taken into consideration for future studies. Finally, these findings suggest that examining moderation by sex may reveal sex-differentiated patterns in the relation between RSA reactivity and children's behavioral outcomes.

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Fig. 1.

Mean resting RSA over time based on pretreatment resting RSA groups. Low and high groups ($n = 16$) were created for the top and bottom 33% of pretreatment resting RSA values. Low group $n = 10$ (posttreatment and follow up), and high group $n = 11$ (post-treatment) and $n = 8$ (follow up). *RSA* respiratory sinus arrhythmia. Significant interaction between Pretreatment resting RSA $\times$ Time, $p = .0003$

Fig. 2.

Mean RSA Reactivity over time by pretreatment resting RSA groups. *RSA* respiratory sinus arrhythmia. Reactivity scores = RSA during trauma script-resting RSA. Negative reactivity scores indicate RSA or vagal withdrawal and positive reactivity scores indicate RSA or vagal augmentation in response to trauma-related script. Low and high groups ($n = 16$) were created for the top and bottom 33% of pre-treatment resting RSA values. Low group $n = 10$ (posttreatment and follow up), and high group $n = 11$ (posttreatment) and $n = 8$ (follow up). Significant interaction between pretreatment resting RSA $\times$ Time, $p = .01$

Fig. 3.

Sex differences in RSA reactivity across time. For females, $n = 20, 13, 12$, and for males $n = 28, 17, 15$, at pretreatment, posttreatment and follow up respectively. *RSA* respiratory sinus arrhythmia. Reactivity scores = RSA during script-resting RSA. Negative reactivity scores indicate RSA or vagal withdrawal and positive reactivity scores indicate RSA or vagal augmentation in response to trauma-related stimulus. Significant interaction between Sex $\times$ time, $p = .03$

Fig. 4.

PTSD symptoms over time by pretreatment resting RSA groups. Low and high groups ($n = 16$) were created for the top and bottom 33% of pretreatment resting RSA values; low group $n = 10$ (posttreatment and follow up), and high group $n = 11$ (posttreatment) and $n = 8$ (follow up). *RSA* respiratory sinus arrhythmia, *CPSS* Child PTSD Symptom Scale. CPSS Scores were measured as a joint child + parent score. Main effect of time, $p < .0001$

Table 1

Demographics of 48 participants with physiological data

Characteristic	<i>n</i> or M	% or SD
Males, <i>n</i> (%)	28	58.3
Females, <i>n</i> (%)	20	41.7
Race		
Black, <i>n</i> (%)	24	50.0
White, <i>n</i> (%)	18	37.5
Mixed, <i>n</i> (%)	6	12.5
Age (year), mean $\pm$ SD	9.7	± 1.9
Maternal age (year), mean $\pm$ SD	42.2	± 12.2
Maternal education (year), mean $\pm$ SD	14.0	± 3.0
Paternal age (year), mean $\pm$ SD	40.0	± 8.9
Paternal education (year), mean $\pm$ SD	12.3	± 2.3
Father lives with child, <i>n</i> (%)	9	18.8
Primary type of trauma		
Natural disaster, <i>n</i> (%)	6	12.5
Witnessed domestic violence, <i>n</i> (%)	14	29.2
Attacked/beaten, <i>n</i> (%)	2	4.2
Sexual, <i>n</i> (%)	10	20.8
Threatened with weapon, <i>n</i> (%)	1	2.1
Bad accident, <i>n</i> (%)	1	2.1
Witnessed murder, <i>n</i> (%)	4	8.3
Seen dead body, <i>n</i> (%)	10	20.8
#Types traumas—parent report, median (Range)	2.5	(1–8)
#Types traumas—child report, median (Range)	2.5	(1–7)
PTSD symptoms—child + parent score, mean $\pm$ SD	14.1	± 8.6
Days since last trauma, mean $\pm$ SD	808.4	± 742.7
Drug group (DCS), <i>n</i> (%)	14	29.2

DCSD-cycloserine, *Drug Group* children randomized to DCS

Table 2

Correlations between RSA variables and demographics

	Resting RSA		RSA reactivity		PTSD symptoms		Age	Sex	Race	#Traumas	Time since trauma	DCS	Med	Cmed
	Posttx	Follow up	Pretx	Posttx	Follow up	Pretx	Posttx							
Resting RSA														
Pretx	0.66**	0.53**	-0.43**	-0.18	0.10	-0.05	-0.09	-0.12	-0.06	0.15	-0.06	0.14	0.01	-0.14
Posttx		0.57**	-0.29	-0.44*	0.12	0.04	-0.04	0.08	-0.13	0.24	-0.08	0.09	0.11	-0.06
Follow up			-0.07	0.03	-0.22	-0.02	-0.15	-0.24	-0.29	0.13	-0.20	0.13	-0.01	-0.04
RSA reactivity														
Pretx				0.44*	0.14	0.13	-0.03	-0.09	0.09	0.06	0.03	-0.06	0.19	0.36*
Posttx					0.18	-0.29	-0.20	-0.42*	-0.02	0.44*	0.10	-0.30	0.10	0.03
Follow up						-0.21	-0.16	-0.12	0.06	0.52**	0.24	0.11	0.07	0.08
PTSD symptoms														
Pretx						0.63**	0.75**		-0.05	0.07	-0.01	0.20	-0.11	0.00
Posttx							0.87**		0.20	0.16	0.01	0.36*	-0.03	0.05
Follow up									0.17	-0.04	0.00	0.28	0.04	0.08
Age										0.05	0.032*	-0.02	0.15	0.18
Sex									0.25	-0.08	-0.01	0.12	-0.22	-0.14
Race									0.00	0.05	0.00	-0.09	-0.07	0.09
#Traumas										0.030	0.11	0.02	0.22	0.18
Time since trauma												-0.01	0.18	0.13

Time since trauma = days since last primary trauma. PTSD symptoms = child + parent joint CPSS score. Race coded as 0 = white, 1 = non-white (African American and Mixed). Sex coded as 0 = male, 1 = female. DCS = randomized to D-cyloserine. Med = medication. Cmed = medication affecting cardiovascular function

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

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

Table 3

Repeated measures mixed model analysis of resting RSA and RSA reactivity

Resting RSA	Estimate	SE	t	P
Model 1				
Time	1.15	0.32	3.59	.001
Pretx resting RSA	1.21	0.13	9.05	<.001
Time × Pretx resting RSA	−0.26	0.07	−3.89	<.001
Model 2				
Time	1.15	0.32	3.58	.0001
Pretx resting RSA	1.26	0.14	9.25	<.001
Sex	1.00	0.62	1.62	.11
Time × sex	−0.09	0.08	−1.13	.27
Pretx resting RSA × sex	−0.19	0.12	−1.57	.12
Time × Pretx resting RSA	−0.25	0.07	−3.79	<.001
RSA reactivity	Estimate	SE	t	P
Model 1				
Intercept	1.83	0.6382	2.86	.006
Time	−0.75	0.64	−2.42	.02
Pretx resting RSA	−0.41	0.31	−3.11	.03
Time × Pretx resting RSA	0.16	0.07	2.42	.02
Model 2				
Intercept	1.7	0.63	2.69	.01
Time	−0.86	0.30	−2.88	.006
Pretx resting RSA	−0.38	0.13	−2.97	.005
Sex	0.13	0.59	0.22	.83
Cmed	0.15	0.07	2.07	.04
Time × sex	0.17	0.07	2.28	.03
Pretx resting RSA × sex	−0.05	0.12	−0.38	.70
Time × Pretx resting RSA	0.16	0.06	2.64	.01
Model 3				
Intercept	1.46	0.74	1.97	.055
Time	−0.73	0.38	−1.95	.057
Pretx resting RSA	−0.33	0.15	−2.19	.03
Sex	0.77	1.28	0.60	.55
Cmed	0.15	0.07	2.08	.04
Time × sex	−0.18	0.62	−0.29	.77
Pretx resting RSA × sex	−0.18	0.26	−0.68	.50
Time × Pretx resting RSA	0.14	0.08	1.74	.09
Time × Pretx resting RSA × sex	0.07	0.13	0.56	.57
Model 4				
Intercept	1.75	0.61	2.89	.006

Resting RSA	Estimate	SE	t	P
Time	−0.85	0.30	−2.87	.006
Cmed	0.15	0.08	2.07	.044
Pretx resting RSA	−0.39	0.12	−3.18	.003
Sex	0.48	0.59	0.82	.42
Time × sex	0.17	0.07	2.32	.02
Time × Pretx resting RSA	0.16	0.06	2.62	.01