



Respiratory Sinus Arrhythmia Change during Trauma-Focused Cognitive-Behavioral Therapy: Results from a Randomized Controlled Feasibility Trial

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Accepted: 1 June 2022 / Published online: 11 June 2022

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Abstract

Trauma-Focused Cognitive-Behavioral Therapy (TF-CBT) is a well-established treatment for pediatric posttraumatic stress disorder (PTSD). Animal-assisted therapy (AAT) has been proposed as an adjunct to TF-CBT that may improve treatment effects through enhanced targeting of affect regulation, as indexed by specific changes in the respiratory sinus arrhythmia (RSA). The current study reports results from a randomized controlled feasibility trial ($N=33$; $M_{age}=11.79$ [$SD=3.08$]; 64% White; 67% female) that measured RSA during Sessions 1, 4, 8, and 12 of a twelve-session TF-CBT protocol and tested whether: 1) TF-CBT + AAT achieved higher average RSA amplitudes relative to TF-CBT alone, and 2) RSA regulation, defined as less variability around person-specific RSA slopes during treatment, explained variation in post-treatment PTSD symptoms. Multilevel modeling failed to support an effect for TF-CBT + AAT on RSA amplitudes ($\delta_{001}=0.08$, $p=0.844$). However, regardless of treatment condition, greater RSA withdrawal was observed within Sessions 4 ($\gamma_{11}=-.01$, $p<.001$) and 12 ($\gamma_{13}=-.01$, $p=.015$) relative to the Session 1 baseline. The average level of RSA amplitude in Session 8 was also significantly lower compared to Session 1 ($\gamma_{02}=-0.70$, $p=.046$). Intraindividual regression models demonstrated that greater RSA regulation predicted improved PTSD symptoms at post-treatment after adjusting for pre-treatment levels ($b_3=20.00$, $p=.012$). These preliminary results offer support for future confirmatory trials testing whether affect regulation, as indexed by changes in RSA, is a mechanism of action for TF-CBT in the treatment of pediatric PTSD.

Keywords Trauma-focused cognitive-behavioral therapy · Respiratory sinus arrhythmia · Mechanisms of action · Posttraumatic stress disorder · Randomized controlled trial

Trauma-Focused Cognitive-Behavioral Therapy (TF-CBT; Cohen et al., 2017) is a skills training and exposure-based behavioral intervention for the treatment of pediatric

posttraumatic stress disorder (PTSD). TF-CBT is the most well-researched (John-Baptiste Bastien et al., 2020) and widely-disseminated (Ebert et al., 2012) behavioral

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intervention for pediatric PTSD. Nearly two dozen randomized controlled trials, conducted by treatment developers (Cohen et al., 2004; Deblinger et al., 2011) and independent investigators (Dorsey et al., 2020; Murray et al., 2015), have consistently demonstrated TF-CBT's superiority in treating pediatric PTSD. TF-CBT is effective across a range of child maltreatment types (Cohen et al., 2011a; Webb et al., 2014), for children exposed to multiple or ongoing traumas (Cohen et al., 2011b; Goldbeck et al., 2016), and for children who present with complex PTSD (Ross et al., 2021; Sachser et al., 2017). This evidence has resulted in TF-CBT being designated as a first-line (Cohen et al., 2010) and well-established (Dorsey et al., 2017) treatment for pediatric PTSD.

Research establishing the mechanisms for how TF-CBT improves pediatric PTSD is only now emerging. One proposed mechanism of action (MOA) is the targeting of affect regulation that, if engaged, could subsequently improve PTSD symptoms. One affect regulation target, out of many implicated in the etiology of PTSD (Nemeroff, 2016), comes from polyvagal theory (Porges, 2003), which asserts that the myelinated branch of the vagus nerve exerts inhibitory control over cardiac activity at the sinoatrial node of the heart via the parasympathetic nervous system. Vagal influence, relative to sympathetic influence, is the primary source of control of cardiac activity during tonic or resting conditions, a phenomenon referred to as the vagal brake (Porges et al., 1996). This brake is withdrawn under phasic conditions such as threat or challenge, resulting in greater sympathetic influence of cardiac activity to resolve the threat. Once resolved, the vagal brake is re-engaged to promote regulation and restore cardiac activity to a relaxed state. These dynamic changes before, during, and after threat have led to a conceptualization of vagal influence as an index of a broader set of affect regulation processes implicated in the etiology of multiple psychiatric disorders (Beauchaine & Thayer, 2015), including PTSD (Porges, 2021). Specifically, impairments in the regulatory dynamics of vagal activity, namely weaker amplitudes at rest and greater withdrawal during challenge, can result in persistent excitation of sympathetic influences on cardiac output, producing hyper-vigilance, hyperarousal, as well as mood and affective states consistent with PTSD presentations (Blechert et al., 2007; Sack et al., 2004; Schneider & Schwerdtfeger, 2020). Prior research has shown impairments in the regulatory dynamics of vagal activity for individuals with PTSD using the respiratory sinus arrhythmia (RSA), a non-invasive index of the variability in vagally-mediated influences on cardiac activity during inhalation and exhalation (Berntson et al., 1997), where lower RSA amplitudes are observed under tonic conditions (Campbell et al., 2019) and greater RSA withdrawal is observed under phasic conditions (Campbell & Wisco, 2021). These regulatory impairments are associated with trauma exposure, including child maltreatment (Dale et al., 2018;

Miskovic et al., 2009), particularly in the context of a current psychiatric disorder (Sigrist et al., 2021). Thus, improvements in the regulatory dynamics of RSA, such as higher amplitudes and reduced withdrawal, may be good indicators of target engagement, that is, a factor changed by an intervention that in turn results in improved clinical outcomes (Sheeran et al., 2017). If so, this can establish affect regulation, as indexed by improvements in RSA, as a MOA for TF-CBT in the treatment of pediatric PTSD.

TF-CBT has the potential to improve the regulatory dynamics of RSA during three phases of active treatment: stabilization, trauma narration and processing, and consolidation (Cohen & Mannarino, 2015). The stabilization phase promotes the acquisition and use of skills, such as relaxation and affect regulation, which may enhance parasympathetic control of the heart through increases in RSA amplitude (Lewis et al., 2015). The trauma narration phase encourages the child to use acquired skills during imaginal exposure exercises. Using acquired skills can regulate the magnitude of RSA withdrawal during exposure exercises (Gray et al., 2018) and subsequently facilitate extinction learning, a key feature of PTSD etiology (Jenness et al., 2019) and treatment (Deblinger et al., 2011). The consolidation phase involves discussing the index trauma with a supportive caregiver to promote generalization of treatment gains, completing in vivo exposure exercises, and planning for future safety. Completing the consolidation phase continues the use of acquired skills and exposure exercises while promoting access to caregiver support, a feature that can also enhance RSA amplitude (Perry et al., 2013). Finally, TF-CBT uses repeated and gradual exposure in every treatment session, a feature that could promote stable change in RSA throughout active treatment. Thus, TF-CBT has the potential to change different aspects of RSA during treatment, which, if linked to improvements in PTSD, have the potential to establish affect regulation as a MOA for this intervention.

Unfortunately, few clinical trials have directly examined or established whether TF-CBT, or similar behavioral interventions, leads to improvements in the regulatory dynamics of RSA that in turn explain improvements in pediatric PTSD. Vagal nerve stimulation can increase RSA amplitude for adults diagnosed with PTSD (Lamb et al., 2017) and animal research has shown that this procedure enhances extinction learning and improves PTSD-like symptoms in rats (Noble et al., 2017; Souza et al., 2019). In an open trial examining the effects of cognitive-behavioral therapy for pediatric PTSD, Lipschutz et al. (2017) examined whether tonic and phasic estimates of RSA changed significantly across pre-treatment, post-treatment, and 3-month follow-up assessments and whether pre-treatment tonic RSA was associated with improvements in PTSD. Results indicated that pre-treatment tonic RSA predicted subsequent changes in RSA, however, no measure of RSA predicted PTSD

symptom improvement. Thus, based on the existing evidence, it remains unclear whether different aspects of RSA can be changed significantly during active treatment for pediatric PTSD and whether any resulting changes in RSA are associated with improvements in PTSD endpoints following treatment.

Animal-assisted therapy (AAT), where an animal is included in the delivery of a treatment to enhance treatment effects or participation in treatment (Chandler, 2005), may be a useful adjunct to TF-CBT to promote change in the regulatory dynamics of RSA for the pediatric population (Parish-Plass, 2008; Reichert et al., 2016). Specifically, AAT may further regulate RSA withdrawal during gradual or imaginal exposure exercises when combined with TF-CBT, something that is believed to allow for longer durations of exposure to achieve desired clinical endpoints with children (Reichert et al., 2016; Tedeschi et al., 2015). Indeed, there is limited evidence suggesting that animals, specifically dogs, can reduce subjective distress in children during other situations involving trauma recall, such as forensic interviews (Krause-Parello & Gulick, 2015). Reducing the magnitude of RSA withdrawal during trauma recall may occur as a result of sensory reinforcement, such as reductions in distress that result from touching or holding the animal, or through brief distraction from the conditioned stimuli eliciting the distress, as observed with adults (Sack et al., 2008). Thus, adding an animal to standard TF-CBT may further engage RSA, specifically by yielding higher overall RSA amplitudes during treatment via reduced RSA withdrawal, and subsequently improve PTSD symptoms by allowing the child to participate more fully in each of three TF-CBT treatment phases. However, there are few existing clinical trials on AAT, either as a stand-alone intervention or as an adjunct, to establish its feasibility and efficacy for changing RSA and improving pediatric PTSD.

The current study reports results from a randomized controlled feasibility trial evaluating the preliminary effectiveness of AAT as an adjunct to standard TF-CBT (TF-CBT + AAT) in the treatment of pediatric PTSD following child maltreatment (Allen et al., 2021). The current trial addresses several gaps in the existing literature. One, while prior research has examined whether tonic and phasic RSA estimates change across pre-treatment, post-treatment, and follow-up (Lipschutz et al., 2017), the current trial measured RSA during active treatment. Research on the treatment of adult PTSD has demonstrated significant within-session increases in RSA amplitude (Sack et al., 2008), a measurement approach that may provide enhanced detection of treatment-related RSA changes linked to improvements in PTSD symptoms. Two, within-session RSA was measured across key treatment sessions delivered according to the standard 12-week TF-CBT protocol (Cohen et al., 2017): 1) Session 1, which served as a treatment baseline from which

to evaluate subsequent changes in RSA; 2) Session 4, or the last session of the stabilization phase; 3) Session 8, or the last session of the trauma narration phase; and 4) Session 12, or the final session of the consolidation phase. Finally, the current study examined RSA dynamics (amplitude, withdrawal, and regulation) during active treatment, leading to two different hypotheses. One, it was hypothesized that, while RSA would withdraw during active treatment due to trauma recall (e.g. exposure) in each treatment arm, TF-CBT + AAT would lead to higher RSA amplitudes relative to TF-CBT. This hypothesis was tested by modeling within-session changes in RSA and testing whether those changes, on average, varied across subsequent treatment sessions (withdrawal) and treatment conditions (amplitude). Two, it was expected that greater RSA regulation, defined as less variability around person-specific RSA slopes during treatment, would explain variation in improved PTSD symptoms.

Methods

Sample

Participants presented to a single behavioral health outpatient clinic affiliated with an academic medical center and specializing in the treatment of psychiatric disorders for children exposed to maltreatment. Inclusion criteria were: 1) a child 6 to 17 years of age exposed to at least one instance of physical abuse, sexual abuse, and/or inter-partner violence as reported by a primary caregiver; 2) participation of a primary caregiver who was not the identified perpetrator of maltreatment; and 3) a caregiver-reported score of ≥ 32 on a PTSD symptom severity screen. Exclusion criteria were: 1) an estimated child IQ < 80 as assessed with the Kaufman Brief Intelligence Test; 2) an autism spectrum diagnosis or diagnosed developmental delay; 3) a current safety concern requiring a higher level of psychiatric care, such as active suicidal ideation; and 4) an uncontrolled allergy to dogs, a fear or dislike of dogs, or a history of aggression toward animals. Child racial demography for the sample was 64% White, 21% Black, and 15% Multi-racial. Ethnic representation was 21% Hispanic. Average child age was 11.79 years ($SD=3.08$) with 67% of participants identifying as female. See Allen et al. (2021) for a complete description of both child and caregiver demographics.

Procedure

Participants were recruited using two strategies. One, staff clinicians identified potentially eligible participants by consecutively screening all families requesting behavioral health services during standard clinic admission procedures. Potentially eligible participants were referred to research

staff who contacted the families to determine interest in trial participation and formally evaluate inclusion and exclusion criteria. Two, caregivers contacted research staff directly after responding to various recruitment materials posted in local community and medical centers. Seventy-five families were identified as potentially eligible trial participants. Twenty-one of these families failed to meet all inclusion criteria or did meet at least one exclusion criterion. Of the 54 remaining families, 21 declined to participate. This resulted in $N=33$ families who met all eligibility criteria and who were invited to complete a formal pre-treatment assessment. Upon arrival at the pre-treatment assessment, research assistants explained all study procedures to each family member prior to obtaining written informed consent and assent. Families completing the pre-treatment assessment were informed that they would receive one of two treatments in this trial: one that included a complete administration of an already well-established intervention (TF-CBT) or one that included a complete administration of the same well-established intervention with a trained service animal in the treatment sessions (TF-CBT + AAT). Each family member was informed that the treatment they would receive was determined at random (i.e. “like flipping a coin”) and they would be notified after the pre-treatment assessment which treatment they would receive. The 33 families completing the pre-treatment assessment were then randomly assigned to treatment condition, constituting the intent-to-treat sample used for subsequent analysis. Of these 33 families, $n=29$

provided reliable electrocardiogram (ECG) data needed to generate RSA estimates (see Fig. 1).

A two-arm, parallel groups, randomized controlled trial tested the preliminary effectiveness of TF-CBT + AAT relative to TF-CBT alone. Participants were randomly assigned to treatment conditions using a blocked randomization procedure stratified by gender (male, female) and age (6–11, 12–17) categories. The study statistician generated the randomization sequence prior to trial initiation. The study statistician and research investigators were masked to participants’ assigned treatment condition. Two Master’s-level clinicians completed independent training and certification requirements for delivering TF-CBT. Clinicians delivered treatment in both trial arms and were randomly assigned to provide either TF-CBT + AAT or TF-CBT alone when initiating treatment with a new participant. Each arm of the RCT followed the standard TF-CBT treatment protocol administered over 12 weekly sessions with each session lasting 90 min in duration and split equally among children and the primary caregiver. ECG recordings were obtained during the 45-min child portion of the 90-min treatment session.

The TF-CBT + AAT arm involved contracting with a local organization that provided trained dogs for administering the AAT adjunct. Clinicians first met with the specific dogs that would participate in the trial and were trained in identifying canine body language to recognize signs of comfort or distress as well as in providing cues to the dog, such as prompting it to sit or move away. Prior to initiation of the

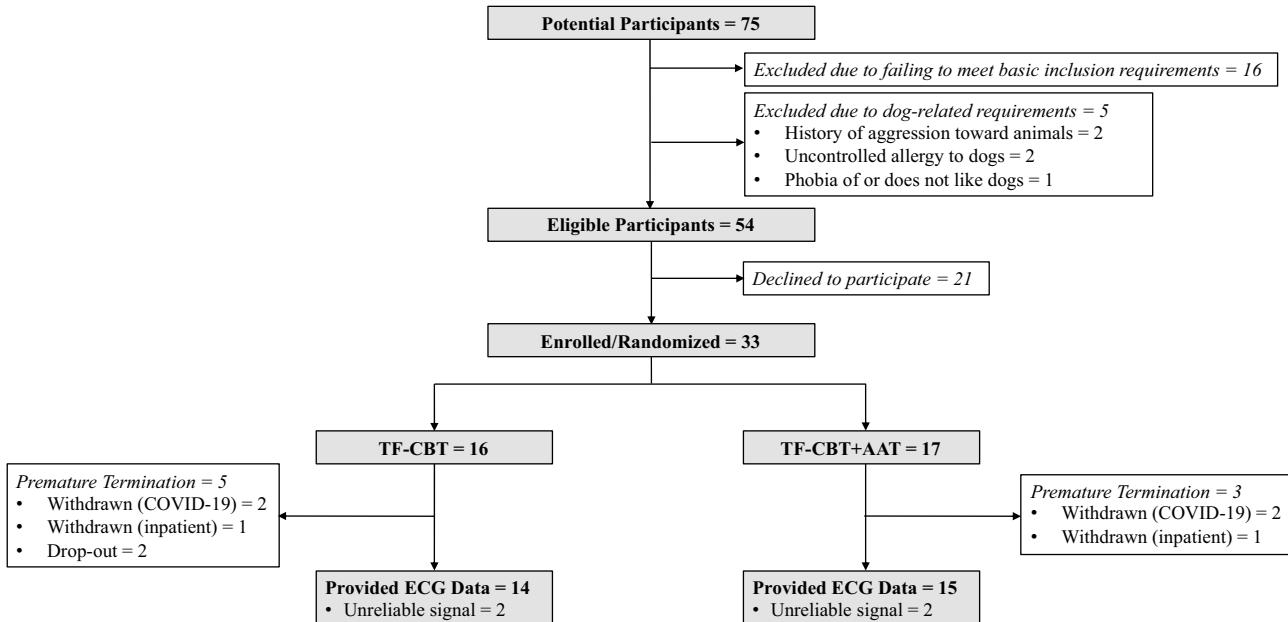


Fig. 1 CONSORT diagram

trial, clinicians rehearsed integrating dogs into delivery of TF-CBT during mock pilot sessions with volunteer children 6 to 17 years of age who were not part of the trial. Dogs participating in the trial were required to be in the treatment room for all treatment sessions; however, the level of child engagement with dogs during treatment sessions was based on the child's preference and comfort. During situations when the child appeared distressed, clinicians were instructed to offer the dog as a means of coping, along with a prompt to use an appropriate TF-CBT skill. At no other time were the dogs deliberately introduced into the activities of the treatment session. All TF-CBT + AAT treatment sessions were observed through a one-way mirror by trained dog handlers.

RSA was measured during Sessions 1, 4, 8, and 12 for both the TF-CBT + AAT and TF-CBT arms. Session 1 involved an introduction to TF-CBT, a review of the index trauma leading to the request for services, and delivery of psychoeducation regarding common reactions to trauma exposure. This session therefore serves as a treatment baseline as the primary agents of change in TF-CBT, that is, skills acquisition, trauma narrative and processing, and consolidation have not been delivered. Session 4 involved the delivery of skills for recognizing the bidirectional relations among cognitions, affect, and behavior and how these processes are affected by the index trauma. Session 4 also represented the completion of the stabilization phase of TF-CBT, where participants learned a variety of skills for promoting relaxation and affect regulation and were encouraged to use those skills when reminded of the index trauma. Session 8 involved the completion of an imaginal exposure exercise, where the participant created a factual narrative of the index trauma that involved the specific cognitions, affect, and physical sensations experienced during the trauma, and engagement of cognitive restructuring to challenge and repair any identified distortions about the trauma. Session 8 also represented the completion of the trauma narration and processing phase of TF-CBT. Finally, Session 12 represented the final session of the treatment protocol that included reviewing progress made during the course of TF-CBT and planning for the participant's future safety. Session 12 also represented the completion of the consolidation phase of TF-CBT, where the participant shares their trauma narrative with a caregiver and where any in vivo exposure exercises have been identified and executed. While these sessions represent key aspects of delivering TF-CBT and how various phases of TF-CBT may impact RSA, it is important to note that gradual exposure to conditioned stimuli is delivered in every session of TF-CBT. Gradual exposure is administered via therapeutic discussions about the index trauma, the application of skills for regulating trauma-induced changes in affect and physiology, the

creation of the trauma narrative and subsequent cognitive restructuring, and discussion of the trauma with a caregiver.

Measures

Respiratory Sinus Arrhythmia (RSA). Participants were connected to an ambulatory, three-lead electrocardiogram (ECG) using the Biolog 3991x/4-GPP system (UFI, Inc., Morro Bay, CA) before completing a 10-min "warm up" to habituate to the ECG equipment at each session. Disposable Ag/AgCl electrodes were placed on the chest and abdomen of each participant to acquire an ECG signal. Resulting ECG data streams were amplified and sampled at 1 kHz before applying a QRS peak detection algorithm to quantify inter-beat intervals (IBIs), the time measured in milliseconds between heart contractions. IBIs were subsequently transferred to a computer via USB for later inspection. CardioEdit software (Brain-Body Center, University of Illinois at Chicago, 2007) was used to visually inspect and edit IBI streams for artifacts. Editing consisted of integer arithmetic, such as dividing intervals when detections are missed or adding intervals when spuriously invalid detections occur. After editing IBI data streams, CardioBatch Plus software (Brain-Body Center for Psychophysiology and Bioengineering, University of North Carolina, Chapel Hill, 2016) was used to quantify RSA amplitude in 30-s epochs using the following steps (Porges, 1985; Porges & Bohrer, 1990): 1) timing sequential R-R (beat to beat) intervals to the nearest millisecond to produce heart rate periods; 2) producing time-based data by resampling sequential R-R intervals into 500 ms intervals; 3) detrending the time-based series with a 21-point cubic moving polynomial template to create a detrended residual series; 4) applying a bandpass filter to the detrended time series to extract the variance in the heart period pattern associated with spontaneous breathing in children and adolescents (0.12–1.04 Hz) while eliminating variance outside this range; and 5) using a natural logarithm to transform the variance estimates and normalize the distribution of resulting RSA estimates. Prior research has established this approach for detecting vagal influences in cardiac activity independent of trend and other moderating factors, including respiration, even when compared to other methods of quantifying RSA (Lewis et al., 2012).

UCLA PTSD Reaction Index for DSM-5 (RI-5). The child and adolescent self-report version of the RI-5 (Pynoos & Steinberg, 2015) was administered to assess the frequency of PTSD symptoms present in the past month. Twenty-seven items assess PTSD symptoms according to DSM-5 PTSD diagnostic criteria and are ranked on a five-point Likert-scale (0 = none of the time to 4 = most of the time). Total PTSD symptom severity scores are then generated from these items. Prior versions of the UCLA PTSD Reaction Index have demonstrated strong psychometric

properties for the child and adolescent version of this instrument (Steinberg et al., 2013). Recent evidence for the RI-5 with a trauma-exposed, treatment-seeking sample indicates an internal consistency of Cronbach's $\alpha=0.96$, diagnostic accuracy via the area under the receiver operating characteristic curve = 0.94, and sensitivity (1.00) and specificity (0.86) when compared to gold-standard, clinician-administered interviews (Kaplow et al., 2020). Child and adolescent reported PTSD symptoms at pre-treatment and post-treatment were included in the current study to assess whether change in RSA during the active treatment phase predicted post-treatment PTSD symptoms after adjusting for pre-treatment PTSD levels. Internal consistency of the RI-5 PTSD symptom items in the current sample was Cronbach's $\alpha=0.89$ at pre-treatment and Cronbach's $\alpha=0.94$ at post-treatment. Of note, one child randomly assigned to treatment condition did not complete a pre-treatment assessment of self-reported PTSD symptoms. When the missing data from this one participant is combined with the eight participants that did not complete a post-treatment assessment (see Fig. 1), the remaining sample size for models of PTSD symptoms is $n=24$ ($33 - 1 - 8 = 24$).

Data Analytic Strategy

All data were analyzed in R (R Core Team, 2020). Because each person had multiple RSA measurements, a three-level multilevel model, with RSA assessments nested within Session and Session nested within trial participant, was estimated to account for multilevel correlations. For the first hypothesis, a time indicator was constructed where the first RSA assessment within each session was coded as 0 and counted consecutively until the final assessment for each patient. Session was included in the model as a moderator to differentiate between the same times occurring within each session (e.g., Time 0 in Session 1 and Time 0 in Session 12). RSA was estimated during the first 45 min of each Session and values collected outside of this time limit were removed (1.4% of data). Because RSA was collected every 30 s, the time variable was divided by two so that the time scale matched the length of Session (i.e., 0–45 in 0.5 increments). The repeated RSA assessments were modeled with random intercepts, where RSA was nested within Session and trial participants, and Session was nested within trial participants, using the lme4 package in R, as follows:

$$RSA_{tsi} = \beta_{0_{si}} + \beta_{1_{si}}(Time_{tsi}) + \varepsilon_{tsi},$$

where $\beta_{0_{si}}$ is the person- and session-specific intercept that indicates the average value of RSA for person i at the first assessment in Session 1; $\beta_{1_{si}}$ is the linear rate of change in RSA across Session 1; and ε_{tsi} is the occasion-specific

residual, which is distributed $\varepsilon_{tsi} \sim N(0, \sigma^2)$. In turn, the person- and session-specific intercepts were modeled as follows:

$$\beta_{0_{si}} = \gamma_{00_i} + \gamma_{01} * I(Session4_{si}) + \gamma_{02} * I(Session8_{si}) + \gamma_{03} * I(Session12_{si}) + U_{0_{si}},$$

where γ_{00_i} is the person-specific intercept that indicates the expected value for RSA for person i in Session s ; γ_{01} is an indicator (I is an indicator function for binary variable) for the average difference in RSA between Sessions 4 and 1; γ_{02} is an indicator for the average difference in RSA between Sessions 8 and 1; γ_{03} is an indicator for the average difference in RSA between Sessions 12 and 1; and $U_{0_{si}}$ are the individual/session differences distributed as $U_{0_{si}} \sim N(0, \tau^2_{00})$. Differences in linear slope across Sessions was modeled as:

$$\beta_{1_{si}} = \gamma_{10} + \gamma_{11} * I(Session4_{si}) + \gamma_{12} * I(Session8_{si}) + \gamma_{13} * I(Session12_{si})$$

where γ_{10} is the linear rate of change in RSA for Session 1; γ_{11} is the difference in the rate of change of RSA between Session 1 and Session 4; γ_{12} is the difference in the rate of change of RSA between Session 1 and Session 8; and γ_{13} is the difference in the rate of change of RSA between Session 1 and Session 12. Finally, the person-specific intercepts were modeled as:

$$\gamma_{00_i} = \delta_{000} + \delta_{001} * I(Treatment_i) + v_{0i},$$

where δ_{000} is the prototypical intercept, δ_{001} is an indicator reflecting average differences in RSA amplitude between the TF-CBT and the TF-CBT + AAT groups; and v_{0i} captures other unexplained individual differences that are distributed $v_{0i} \sim N(0, \rho^2_{00})$.

The second hypothesis was addressed using a planned two-step process. In the first step, individual regressions, similar to what is done in N-of-1 or single-case designs, were estimated for each patient with time predicting RSA values, ignoring session, using the dplyr and lm functions in R:

$$RSA_t = \alpha_i + b_i(Time_t) + \varepsilon_i,$$

where α_i is the subject-specific intercept that indicates the level of RSA at time $_t$; b_i is the subject-specific linear rate of change in RSA; and ε_i is a residual term that indicates the difference between the predicted value and the observed value of RSA. ε_i is distributed $\varepsilon_i \sim N(0, \sigma^2)$. The following three features were then extracted from each model for each patient: RSA intercept, RSA slope, and RSA residual standard error (RSE), which is the standardization of the variance of ε_i . Because the RSE is a measure of variability, it can be considered a measure of individual differences in RSA regulation where lower values reflected greater regulation of RSA throughout sessions. In the second step, these RSA features: 1) RSA Intercept; 2) RSA Slope; and 3) RSA

Regulation, were entered together in linear regression models predicting PTSD symptom severity at post-treatment after adjusting for pre-treatment levels and modeled as follows:

$$PTSD_{post} = b_0 + b_{1-3}(RSA \text{ Feature}) + b_4(PTSD_{pre}) + \epsilon_i$$

where b_0 is the average level of PTSD at post-treatment when the RSA Feature is 0 and PTSD at pre-treatment is at the sample average; b_{1-3} is the linear slope for the specific RSA feature (RSA Intercept₁, RSA Slope₂, and RSA Regulation₃); b_4 is the linear relation between pre-treatment PTSD and post-treatment PTSD, and ϵ_i is a residual term of unexplained individual differences.

After examining which RSA features significantly predicted PTSD symptoms at post-treatment, exploratory models then determined whether any of these significant RSA features were driven by: 1) the effects of a specific Session, 2) change during the first two phases of TF-CBT, and 3) change throughout the entirety of treatment. To achieve this, the procedures for the individual regression approach discussed above were replicated within each session (four Sessions per patient). Linear regressions for the session-specific RSA features were first entered into regressions separately (one for each session) and then change scores between Session 1 and each subsequent Session (e.g. Session 8 – Session 1) were included as predictors in separate models to test whether change in RSA features predicted PTSD symptoms at post-treatment. The exploratory models for

hypothesis two have the potential to add insight into whether RSA regulation was influenced by a particular session or if RSA regulation was more strongly influenced during the first two phases of treatment as opposed to the entirety of treatment, results that may aid future research on when exactly RSA regulation is being engaged as a target.

Results

Hypothesis 1: TF-CBT + AAT would Lead to Higher Average RSA Amplitudes

There was not a significant difference between the TF-CBT + AAT and TF-CBT treatment conditions on average level RSA amplitudes during active treatment, $\delta_{001}=0.082$, $p=0.844$. However, additional parameters in this model indicated that systematic between-session change in RSA could be detected during the active treatment phase regardless of treatment assignment. As depicted in Fig. 2, there was a statistically significant positive increase in RSA during Session 1 ($\gamma_{10}=0.01$, $p<0.001$). However, average RSA growth within Session 4 ($\gamma_{11}=-0.01$, $p<0.001$) and Session 12 ($\gamma_{13}=-0.01$, $p=0.015$) was significantly lower compared to growth within the Session 1 baseline, indicating RSA withdrawal. Additionally, the average level of RSA during Session 8 ($\gamma_{02}=-0.70$, $p=0.046$) was significantly lower than the level observed in Session 1 ($\delta_{000}=7.26$, $p<0.001$). See Table 1 for full model results.

Fig. 2 Within- and Between-session Change in the Respiratory Sinus Arrhythmia during Active Treatment. Observed session-level trajectories are in depicted in grey and average session-level predicted trajectories are depicted in black

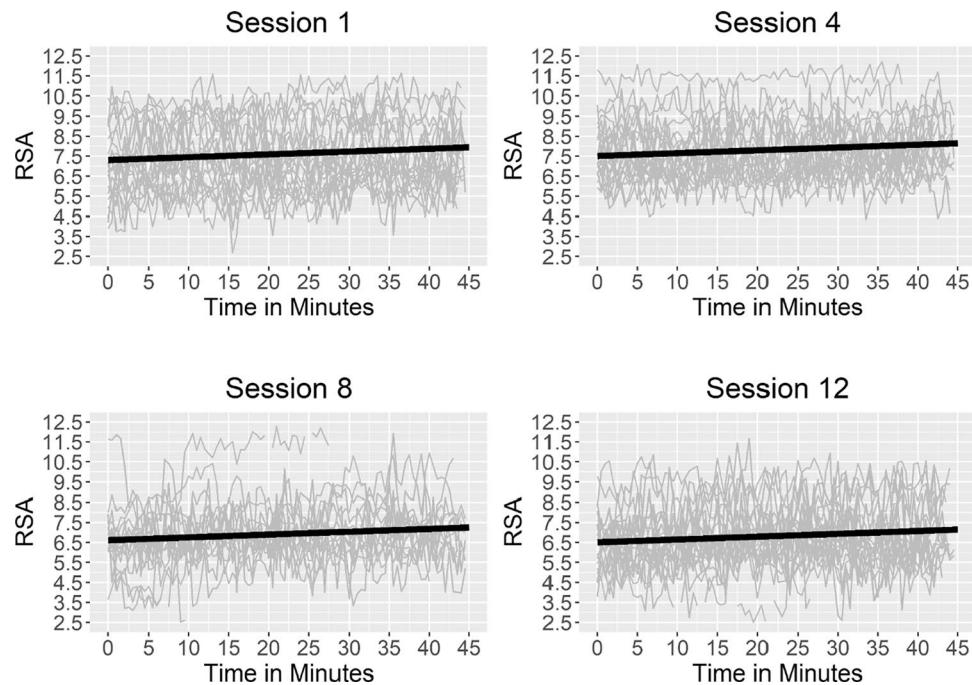


Table 1 Model Results for Detecting Change in RSA during Active Treatment

Fixed Effects	Estimate	SE	p	95% CI	
				Lower	Upper
Intercept (δ_{000})	7.26	0.36	<0.001	6.57	7.95
Group (δ_{001})	0.08	0.41	0.844	-0.71	0.90
Time (γ_{10})	0.01	0.00	<0.001	0.01	0.02
Session 4 (γ_{01})	0.21	0.32	0.500	-0.40	0.83
Session 8 (γ_{02})	-0.70	0.35	0.046	-1.37	-0.03
Session 12 (γ_{03})	-0.80	0.33	0.017	-1.43	-0.17
Session 4 \times Time (γ_{11})	-0.01	0.00	<0.001	-0.01	-0.00
Session 8 \times Time (γ_{12})	0.00	0.00	0.526	-0.00	0.01
Session 12 \times Time (γ_{13})	-0.01	0.00	0.015	-0.01	-0.00
Random Effects (Intercept)	SD				
Within Person (Level 3: v_{0i})	0.90			0.56	1.26
Session Within Person (Level 2: U_{si})	1.04			0.86	1.23
Sigma/Observation (Level 1: ε_{tsi})	0.93			0.91	0.95

Time represents the linear slope for change in RSA during active treatment

SD the standard deviation of the random effect, 95% CI lower lower bound of the 95% confidence interval, 95% CI upper upper bound of the 95% confidence interval

Hypothesis 2: RSA Regulation will Explain Variation in PTSD Symptoms at Post-Treatment

Individual differences in the RSA Intercepts ($b_1 = 3.32$, $p = 0.300$), as well as RSA Slopes during active treatment ($b_2 = -389.93$, $p = 0.412$), were not significantly associated with PTSD symptoms at post-treatment after adjusting for pre-treatment PTSD symptom severity. However, greater RSA Regulation, that is, less variability in RSA change during active treatment, was associated with less severe PTSD symptoms at post-treatment ($b_3 = 20.00$, $p = 0.012$). See Table 2 for full model results. Exploratory models revealed that neither the magnitude of RSA Regulation within any specific Session (p 's > 0.288) nor during the first two phases of TF-CBT (p 's > 0.319) were associated with change in PTSD symptoms. However, the magnitude change in RSA Regulation throughout active treatment, that is, from Session 1 ($M = 0.76$, $SD = 0.38$) to Session 12 ($M = 0.90$, $SD = 0.32$), predicted PTSD symptom improvement at post-treatment ($b_{s12-s1} = 15.59$, $p = 0.020$). See Table 3.

Discussion

Establishing the mechanisms by which TF-CBT and other behavioral interventions for the treatment of pediatric PTSD achieve their effects is an important area of research. Unlike treatment outcome studies that have a primary aim to demonstrate change in identified clinical endpoints, research on one or more mechanisms of action

provides needed scientific evidence on precisely how those effects are achieved and which aspects of the intervention are responsible for achieving them. Without explicit research on such mechanisms, behavioral interventions are essentially “black boxes”, where the processes that change during intervention, and the components of the

Table 2 Intraindividual Regression Models for RSA and Post-Treatment PTSD Symptoms

Parameters	Estimate	SE	p	95% CI	
				Lower	Upper
Model 1					
Intercept (b_0)	30.17	3.74	<0.001	22.32	28.02
RSA Intercept (b_1)	3.32	3.11	0.300	-3.21	9.86
Pre-Treatment PTSD (b_4)	0.87	0.29	0.007	0.27	1.47
Model 2					
Intercept (b_0)	29.14	3.81	<0.001	21.13	37.15
RSA Slope (b_2)	-389.93	464.04	0.412	-1364.84	584.97
Pre-Treatment PTSD (b_4)	0.95	0.29	0.004	0.35	1.55
Model 3					
Intercept (b_0)	26.98	3.34	<0.001	19.97	33.99
RSA Regulation (b_3)	20.00	6.42	0.012	4.50	31.49
Pre-Treatment PTSD (b_4)	1.02	0.24	0.001	0.51	1.53

RSA Respiratory sinus arrhythmia, PTSD Posttraumatic stress disorder

Table 3 Session Level Intraindividual RSA Regulation and Post-treatment PTSD Symptoms

Parameters	Estimate	SE	p	95% CI	
				Lower	Upper
Session 1					
Intercept	30.42	3.75	<0.001	22.32	38.52
RSA Regulation (b_{s1})	-7.97	8.85	0.384	-27.09	11.15
Pre-Treatment PTSD	0.99	0.29	0.004	0.37	1.61
Session 4					
Intercept	30.21	4.16	<0.001	21.35	39.08
RSA Regulation (b_{s4})	-10.63	19.33	0.591	-51.84	30.58
Pre-Treatment PTSD	1.04	0.35	0.010	0.29	1.79
Session 8					
Intercept	30.56	0.50	<0.001	20.85	40.28
RSA Regulation (b_{s8})	7.98	12.58	0.537	-19.19	35.14
Pre-Treatment PTSD	0.89	0.37	0.033	0.08	1.70
Session 12					
Intercept	30.45	3.76	<0.001	22.51	38.39
RSA Regulation (b_{s12})	12.33	11.23	0.288	-11.37	36.02
Pre-Treatment PTSD	0.92	0.28	0.004	0.34	1.51
Session 4 – Session 1 Difference					
Intercept	30.13	4.45	<0.001	20.34	39.92
RSA Regulation (b_{s4-s1})	8.17	11.24	0.482	-16.56	32.90
Pre-Treatment PTSD	1.09	0.33	0.007	0.36	1.81
Session 8 – Session 1 Difference					
Intercept	28.28	4.09	<0.001	19.18	37.38
RSA Regulation (b_{s8-s1})	11.20	10.69	0.319	-12.62	35.07
Pre-Treatment PTSD	0.86	0.36	0.036	0.07	1.66
Session 12 – Session 1 Difference					
Intercept	28.80	2.92	<0.001	22.50	35.09
RSA Regulation (b_{s12-s1})	15.59	5.88	0.020	2.89	28.29
Pre-Treatment PTSD	0.89	0.22	0.002	0.41	1.37

RSA Respiratory sinus arrhythmia, PTSD Posttraumatic stress disorder, Difference the change in intraindividual variability in RSA between the respective treatment sessions

intervention responsible for producing that change, remain unknown (Collins et al., 2009). Instead, research on the mechanisms of action for an intervention can establish putative targets to engage, along with the aspects of the intervention that engage those targets, with the goal of enhancing the effectiveness or efficiency of an established intervention (Shenk et al., 2017). Given the similarities in core components delivered in the majority of behavioral interventions for pediatric PTSD (Dorsey et al., 2017), such continued research on mechanisms of action would have informative value for each of those interventions. The current study examined affect regulation via changes in different dimensions of RSA as a potential MOA for TF-CBT and the adjunctive effects of including AAT during active treatment. Consistent with the target engagement and target validation steps for testing mechanisms of action (Sheeran et al., 2017), the current study hypotheses were to determine: 1) if TF-CBT + AAT achieved higher RSA

amplitudes relative to TF-CBT alone during the active treatment phase, and 2) whether greater regulation of RSA changes during active treatment explained improvements in PTSD symptom severity at post-treatment.

The current study failed to find support for adding AAT to TF-CBT to increase average RSA amplitudes during active treatment. This result is consistent with prior treatment outcome research from this same trial that failed to find increased treatment effects for TF-CBT + AAT (Allen et al., 2021). However, results did demonstrate significant changes in RSA during TF-CBT regardless of treatment assignment. Consistent with prior research (Sack et al., 2008), there was a significant increase in RSA amplitude during Session 1, which served as a baseline for subsequent within-session changes in RSA measured repeatedly during active treatment. Relative to Session 1, there was significantly slower RSA growth within Sessions 4 and 12 of the TF-CBT protocol. There was also a significant reduction in the overall

level of RSA during Session 8. These findings suggest that the active phases of TF-CBT engage RSA in a manner consistent with a withdrawal of vagal activity, a phenomenon that often occurs during recall of a trauma script or narrative (Blechert et al., 2007; Schneider & Schwerdtfeger, 2020) which serves as the foundation for exposure exercises during TF-CBT. TF-CBT introduces gradual exposure exercises at the very beginning of treatment by referencing the index trauma and connecting both presenting complaints and treatment goals to that trauma. This type of gradual exposure continues throughout treatment, including the introduction of relaxation and affect regulation techniques during skills acquisition (Session 4), imaginal exposure during the trauma narrative phase (Session 8), and discussion of the trauma with a supportive caregiver during the consolidation phase (Session 12). Thus, TF-CBT may engage RSA during active treatment and specifically during and after phases involving both gradual and imaginal exposure exercises. Given the use of exposure as a hallmark feature of behavioral interventions for PTSD (Dorsey et al., 2017), greater RSA withdrawal during TF-CBT was not unexpected. In fact, these changes in RSA during TF-CBT may be an indication that patients are actually engaging in treatment as prescribed with the potential to improve subsequent PTSD outcomes.

Models testing the second hypothesis demonstrated that enhanced regulation of RSA change, defined as less variability around person-specific RSA slopes during treatment, predicted improved PTSD symptoms after treatment. This result suggests that gradual changes in RSA during TF-CBT, perhaps through repeated gradual exposure during skills acquisition or the use of skills during imaginal exposure exercises, are associated with therapeutic improvements in subsequent PTSD symptoms. While a withdrawal of RSA is expected under phasic conditions such as trauma recall (Berntson et al., 1997), greater magnitudes of RSA withdrawal have been proposed as a trans-diagnostic marker of several different psychiatric disorders (Beauchaine et al., 2019), including PTSD (Campbell & Wisco, 2021; Porges, 2021). However, using exposure to promote extinction learning is a core component of many behavioral interventions for PTSD (Dorsey et al., 2017) including TF-CBT (Deblinger et al., 2011). Results from the current study suggest exposure may be most therapeutic when individuals effectively regulate the magnitude of RSA withdrawal during treatment. For example, acquiring skills to regulate affective reactions to conditioned stimuli, and using those skills in combination with repeated gradual and imaginal exposure exercises, may limit the magnitude of RSA withdrawal and thereby promote enhanced regulation of RSA change during TF-CBT. Doing so during the course of TF-CBT may keep RSA changes within a degree of variability most conducive to approaching trauma-related conditioned stimuli, thereby

extinguishing conditioned (hyperarousal) and operant responses (avoidance and escape behaviors) and subsequently achieving improvements in PTSD symptoms most effectively. Enhanced regulation of RSA during TF-CBT may therefore serve as one valuable indicator leading to change in PTSD symptoms, as the person-specific level of RSA and linear change in RSA during TF-CBT did not predict subsequent PTSD symptoms (see Table 2).

Several limitations of this study are worth noting. One, the goal of the current trial was to test the feasibility and preliminary effectiveness of adding AAT to standard TF-CBT in the treatment of pediatric PTSD. The results presented here are not based on a fully powered confirmatory trial and therefore results should only be interpreted as preliminary and exploratory. Two, the COVID-19 pandemic limited recruitment and retention efforts with the trial closing completely during active data collection due to human subjects concerns. Third, the current sample included children experiencing an interpersonal trauma (e.g., sexual abuse, physical abuse). While TF-CBT is effective in treating PTSD stemming from both interpersonal and non-interpersonal forms of trauma, it is unclear whether the current results generalize to other types of trauma. Four, RSA was not measured at every treatment session to minimize participant burden, thereby limiting knowledge about RSA change at each session, within specific treatment phases, or continuously across the course of TF-CBT. Five, this study demonstrated RSA withdrawal during TF-CBT and that a greater regulation of RSA during treatment was related to improved PTSD symptoms at post-treatment. However, this study did not evaluate change in vagal functioning or larger autonomic or neural activity implicated as affect regulation mechanisms of PTSD (e.g. Cisler et al., 2015). Direct manipulation of the vagus nerve would be required to demonstrate the regulatory impact of parasympathetic influences on PTSD. Even then, change in parasympathetic influence alone is unlikely to produce all necessary improvements in affect regulation needed to treat PTSD. Instead, the current results suggest that different RSA dimensions are indicators of target engagement in the treatment of pediatric PTSD and serve as potential biomarkers of change in a broader set of affect regulation mechanisms that improve with receipt of a well-established behavioral intervention, such as TF-CBT.

To our knowledge, this is the first study to demonstrate change in RSA during the course of TF-CBT and relate this change to improved PTSD function after completion of treatment. These results provide preliminary support for RSA as a target to engage for TF-CBT in the treatment of pediatric PTSD. However, future research in a fully-powered, confirmatory trial is needed to support this claim and formally test affect regulation as a MOA for TF-CBT. Continued research in this area has the potential to explain how already established and effective behavioral interventions achieve

treatment effects, that such existing interventions can engage novel and critical targets for direct intervention, and spur ways to refine interventions or their components to enhance treatment efficacy.

Acknowledgements Research reported in this manuscript was supported by the National Institutes of Health under Award Numbers R21HD091887 and T32HD101390. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors wish to thank the trial's clinicians, Amy Slenker, LCSW, and Ryan Hagarman, LCSW, as well as all the youth and families that participated in this trial.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing or conflicts of interests.

Ethical Approval All procedures were reviewed and approved by Penn State Hershey Medical Center's Institutional Review Board and an Institutional Animal Care and Use Committee prior to recruitment and data collection.

Informed Consent The trial from which the current study is drawn, and all corresponding hypotheses, were pre-registered at clinicaltrials.gov (NCT03135119).

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