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RESEARCH ARTICLE

Is respiratory sinus arrhythmia a modifiable index of symptom change in cognitive behavioral therapy for youth? A pooled-data analysis of a randomized trial

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Abstract
Objective We evaluated whether respiratory sinus arrhythmia (RSA) reactivity and resting RSA—physiological markers reflecting the increase in heart rate with inspiration and decrease during expiration related to parasympathetic influence on the heart—are modifiable and predict symptom change during youth psychotherapy. **Methods:** Diverse youth (N = 158; ages 7–15; 48.1% female) received the *Modular Approach to Therapy for Children* and completed pre-treatment (pre), post-treatment (post), and 18-months postbaseline (18Mo) assessments. We measured resting RSA, RSA reactivity during stress induction, and psychopathology symptoms. **Results:** Pre-to-post and pre-to-18Mo, reactivity decreased, and resting RSA increased. Changes in reactivity and resting RSA, separately, did not predict reduced psychopathology. Yet, decreased reactivity combined with increased resting RSA predicted reduced psychopathology over time, suggesting that observed RSA changes were beneficial for some. Higher dosage of a module utilizing slow-breathing, muscle-relaxation, and imagery predicted greater pre-to-18Mo changes in reactivity and resting RSA, whereas a similar module with less emphasis on slow-breathing did not. **Conclusions:** Findings raise the possibility that youth reactivity and resting RSA could be modifiable during cognitive behavioral therapy and contribute to the amelioration of psychopathology. More studies are needed to determine whether resting RSA and RSA reactivity are modifiable indices of symptom change in slow-breathing practices and psychotherapy.
ClinicalTrials.gov Identifier NCT03153904, registered May 15, 2017.

Keywords: transdiagnostic; psychotherapy; youths; respiratory sinus arrythmia; slow-breathing

Clinical or methodological significance of this article: If resting RSA and RSA reactivity—physiological indicators reflecting the increase in heart rate with inspiration and decrease during expiration related to parasympathetic influence on the heart —are modifiable and change in tandem with psychological symptom reduction following youth psychotherapy, this may inform future research that seeks to evaluate RSA reactivity and resting RSA as possible mechanisms of change or targets for treatment. In a community effectiveness trial where psychopathology decreased after receipt of cognitive behavior therapy, RSA reactivity decreased and resting RSA increased following treatment, and a higher dose of a module utilizing calming techniques in stressful situations (e.g., slow-breathing, muscle relaxation, and calming imagery) predicted more change in RSA reactivity and resting RSA, whereas a similar home-practice relaxation module with less emphasis on slow-breathing did not. Although changes in RSA reactivity and resting RSA alone were unrelated to symptom changes, decreased RSA reactivity along with increased resting RSA predicted reduced symptoms —raising the testable possibility that RSA reactivity and resting RSA could be modifiable and contribute to the reduction of psychopathology in the context of slow-breathing and cognitive behavioral therapy for youth.

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Levels of youth psychopathology have increased in recent years (Twenge et al., 2019). Meanwhile, effect sizes ($g \sim 0.50$) of treatments for young people have not improved over the last 50 years (Weisz et al., 2019). Identifying moderators and mediators of change may be an important path for moving the needle on the effect sizes of psychological treatments for youth (Weisz et al., 2019). Physiological measures may provide further insight as an objective index that complements self-reported symptoms. One such physiological moderator and/or mediator of symptom change for youth could be respiratory sinus arrhythmia (RSA).

RSA measured at rest reflects the increase in heart rate with inspiration and decrease during expiration related to parasympathetic influence on the heart (Berntson et al., 1997; Thayer et al., 2012), which is indexed from the variability in heart rate within the frequency band associated with respiration. One simplistic yet helpful analogy of parasympathetic influence on the heart is the "vagal brake." At rest, activation of the vagus nerve stimulates longer intervals between heartbeats during exhalation than inhalation, whereas under stress, the vagal brake disengages —allowing the heart rate to increase (Berntson et al., 1997). The ability to rapidly engage and release the "vagal brake" tends to be reflected by high resting RSA and, during stressful situations, high RSA reactivity (i.e., the decrease in RSA during a stressor task) (Berntson et al., 1997; Thayer et al., 2012).

Increases in resting RSA following treatment could indicate an expanded capacity for emotion regulation that leads to reductions in psychopathology. One goal of The *Modular Approach to Therapy for Children with Anxiety, Depression, Trauma, or Conduct Problems* (MATCH-ADTC, or "MATCH") is to help youth foster skills in emotion regulation (Chorpita & Weisz, 2009). High resting RSA is predicted by greater tonic inhibition of the amygdala by the medial prefrontal cortex in adults, which plays a crucial role in the effective regulation of emotion (Thayer et al., 2012). Indeed, high resting RSA is associated with lower levels of internalizing and externalizing psychopathology—including symptoms of anxiety, depression, posttraumatic stress disorder (PTSD), and conduct problems—in youth (Hinnant & El-Sheikh, 2013). Thus, it is possible that increases in RSA may predict improvements in these issues after psychotherapy.

More research on whether and how resting RSA changes and predicts outcomes in psychotherapy in youth across a broader range of psychopathology is needed. Several studies to date have found psychological treatment to predict increases in resting RSA over time in adults (Delgado-Pastor et al., 2015; Garakani et al., 2009). However, research on youth is more limited. One study found resting RSA increased after cognitive behavioral therapy (CBT) in youth with PTSD ages 7–13 ($N = 48$ with 58% retention) (Lipschutz et al., 2017), yet further research with larger samples is needed. As a predictor of treatment response, the evidence seems more mixed. For instance, fourth-grade children with low RSA, compared to their peers with high RSA, were more likely to respond to a CBT intervention for conduct problems (Glenn et al., 2019). However, in another study, adults with *higher* resting RSA were more likely to respond to CBT for PTSD (Soder et al., 2019). Thus, more research is necessary to help reconcile these mixed findings.

Additional research is warranted on how RSA reactivity predicts psychopathology in psychotherapy. RSA reactivity is negatively associated with psychopathology in children across the internalizing and externalizing spectra (Graziano & Derefinko, 2013). Higher levels of RSA reactivity are hypothesized to reflect adaptive shifts in RSA from rest to attention-demanding or challenging tasks by mobilizing the cardiac and metabolic resources to handle it (Graziano & Derefinko, 2013). That said, some studies have found positive associations between RSA reactivity to stress-inducing tasks and psychopathology (Hinnant & El-Sheikh, 2013). As a predictor of treatment response, children with low RSA reactivity may benefit more from treatment because they have more room for improvement. Alternatively, those with high RSA reactivity may be better able to connect with their therapist or learn adaptive emotion regulation strategies and thus derive greater benefit from treatment. Studies are needed on whether and how RSA reactivity predicts treatment response in youth.

We aimed to bridge several gaps. First, more clarification is needed on whether there are changes in resting RSA and RSA reactivity in the context of evidence-based psychological treatment (EBPT). Second, whether such changes, in turn, predict reductions in psychopathology in youth is not fully understood. Certain EBPTs (e.g., mindfulness-based) have exhibited both increased resting RSA and reduced symptoms in adults (Delgado-Pastor et al., 2015), yet less is known about changes in resting RSA and RSA reactivity as predictors of symptom change in youth. If resting RSA and RSA reactivity are modifiable and change with symptom reduction during treatment, these findings could inform future studies that aim to test RSA reactivity and resting RSA as possible mechanisms of change or targets for youth psychotherapy.

An important related question is what therapeutic practices that might lead to changes in RSA. Treatments that incorporate slow-breathing practices could be particularly likely to change RSA reactivity and resting RSA. Slow, deep breathing has been shown to increase RSA in adults (Hunt et al.,

2021). However, the long-term impacts of slow deep breathing practices on RSA reactivity and resting RSA among youth are not clearly understood. Although group CBT plus deep breathing has shown to be inferior to group CBT alone for adults with panic disorder, this may be unique to exposure therapy by inhibiting corrective learning experiences (Schmidt et al., 2000). To the extent that changes in RSA might occur due to slow breathing, it is possible that this therapeutic technique could help alleviate other forms of psychopathology more broadly.

Objectives

In the present study, we investigated changes in RSA and its association with psychopathology among 158 youths who were treated for emotional and behavioral concerns with a transdiagnostic modular cognitive–behavioral EBPT and exhibited decreased psychopathology following treatment. Measures of psychopathology symptoms and RSA were collected at pretreatment, post-treatment, and 18-months postbaseline. We had two pre-registered aims and hypotheses (osf.io/d3ea5). The first confirmatory aim was to investigate whether RSA reactivity changes following MATCH treatment. Based on prior evidence showing that symptom-level gains were achieved at post-treatment and maintained at least 18 months after pre-treatment in youth who received MATCH (Chorpita et al., 2013; Weisz et al., 2012, 2020), we hypothesized that RSA reactivity would increase following treatment and that these gains would be maintained at 18 months postbaseline. The second aim was to investigate RSA reactivity as an index of symptom change. We hypothesized that greater increases in RSA reactivity would predict greater decreases in internalizing and externalizing symptoms.

We also had two preregistered exploratory aims. The first was to examine whether changes in RSA reactivity and resting RSA vary based on whether the modules incorporating slow-breathing exercises (e.g., quick calming) were covered in therapy or their dosage. The second exploratory aim was to examine whether pre-treatment RSA reactivity predicted reductions in internalizing and externalizing symptoms following treatment.

Methods

Participants

The sample included 158 youths referred to one of four community mental health clinics for treatment of emotional and behavioral concerns. Youths received MATCH delivered by therapists in community mental health clinics (Chorpita & Weisz, 2009; Weisz et al., 2020). Inclusion criteria were youths (a) ages 6–15 and their caregivers, (b) seeking services at community mental health clinics, and (c) with primary problem(s) or disorder(s) related to anxiety, depression, traumatic stress, or conduct problems. Exclusion criteria were (a) primary presenting problems not in the scope of MATCH (youths with these problems were included if referred for a MATCH-relevant problem); (b) primary caregiver unwilling to be involved in treatment and complete study assessments; and (c) presence of psychotic spectrum disorders, autism spectrum disorders, eating disorders, intellectual disability, or past-year hospitalization for suicidal thoughts or behaviors. More information is provided in Weisz et al. (2020).

These data were drawn from a randomized controlled effectiveness trial of MATCH (Weisz et al., 2020), testing different levels of implementation support. This study examined the effectiveness of MATCH among community outpatient therapists who either received (a) training in MATCH plus low-cost implementation supports or (b) training in MATCH plus ongoing expert consultation plus the low-cost implementation supports. Youths and clinicians in the study were randomized to two active study conditions—i.e., the same treatment program implemented by clinicians who received two different forms of implementation support. Study analyses showed very similar outcomes for both forms of support and also showed statistically significant symptom reduction in both study conditions on every clinical outcome measure, with average scores at posttreatment in the nonclinical range (Weisz et al., 2020). In other words, the two conditions did not differ in their outcomes, but both exhibited significant reduction from pre- to post-treatment and to 18-month postbaseline (Weisz et al., 2020). Thus, the present analysis pools data from the entire sample, does not include study condition as a covariate, and is reported in accordance with the TREND statement (Des Jarlais et al., 2004).

The original sample included 200 youths who were randomly allocated to condition, received MATCH and completed some level of outcomes assessment. The dosage and duration of MATCH were determined by the clients and their therapists. The mean number of MATCH sessions was 10.78 (SD = 9.28), and the average duration from baseline to the last session was 166.8 days (SD = 135.2). Although participants were paid for every research assessment they completed, no incentives were used to increase adherence. The psychophysiological assessments used in the present analysis were added as a supplemental protocol such that participating families could opt-in to participate in these

assessments, but it was not required for participation in the larger study. Of the 200 in the original sample, 158 (79%) youths completed any supplemental physiological assessments in which RSA was collected. Of these 158, 153 youth (96.8%) completed RSA assessments at baseline, 78 (49.4%) at post, and 94 (59.5%) at 18mo. Missing data is described in Table S1 and Figure 1 (TREND flow diagram). Completers and non-completers of the physiological assessments at post and 18Mo did not differ on any variable used in our analyses at pre-treatment (see Table S2). Details on participant characteristics can be found in Table I.

Procedure

All procedures were approved by two institutional review boards—one affiliated with Harvard University and the other affiliated with the state's Department of Children and Families. The protocol was registered at ClinicalTrials.gov (clinicaltrials.gov/ct2/show/NCT03153904). We obtained informed consent from caregivers and clinicians and assent from youths prior to study enrollment, and any current conflicts of interest were disclosed with study participants. All procedures were performed in compliance with relevant laws and institutional guidelines, and the procedures followed were in accordance with the ethical standards of Harvard University, the state's Department of Children and Families, and the Helsinki Declaration of 1975, as revised in 2000. After baseline symptom assessments, families were invited to complete the optional in-person physiological assessments, including RSA data and Trier tasks described below, conducted by research associates in community settings. We assessed participants' resting RSA and RSA reactivity along with symptoms of psychopathology at pre-treatment, post-treatment, and 18 months after pre-treatment. The study occurred between October 2013 and June 2018. Further details are described in Weisz et al. (2020).

Measures

Internalizing and externalizing symptoms. We assessed internalizing and externalizing problems using the corresponding composite scales on the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001). The CBCL is a 113-item caregiver-report measure. Each item is rated on a 0–2 scale (2 = very/often true). The CBCL is one of the most widely used measures of youth emotional and behavioral problems, and evidence supporting its validity and reliability is extensive (Ebesutani et al., 2010). Age-normed *t*-scores ($M = 50$, $SD = 10$) with established cut-offs (clinical $\geq 63 >$ borderline $\geq 60 >$ typical; Achenbach & Rescorla, 2001) were used in analyses for clinical relevance of results.

Trier social stress test for children. Youths underwent an adapted Trier Social Stress Test for children—a widely used paradigm for youth where one is asked to deliver a 5-min speech on friendship (Seddon et al., 2020). Youths were first connected to the ECG. Then, after collecting resting RSA, they were given 2 min (instead of the standard 5 min) to prepare their speech and were told it would be reviewed by experts on friendship. Then, the video recording was introduced, and they gave the 5-min speech. Youth were seated while RSA was recorded for the entire procedure. The TSST-C was effective at eliciting an increase in anxiety as reported on the Emotions Ratings Scale (Champagne & Stromberg, 2004) (Pre-treatment: Mean Increase (M) = 0.22, 95% CI [0.03, 0.41], $t = 2.31$; Post-treatment: $M = 0.31$, 95% CI [0.12, 0.51], $t = 3.18$; 18-month follow-up: $M = 0.46$, 95% CI [0.24, 0.68], $t = 4.16$). Furthermore, there were no significant differences between any of the timepoints in the rest-to-speech increases in anxiety (pre to post: Mean Difference (M) = 0.09, 95% CI [−0.18, 0.36], $t = 0.67$, $p = .500$; pre-18fup: $M = 0.24$, 95% CI [−0.05, 0.53], $t = 1.62$, $p = .209$; post-18fup: $M = 0.14$, 95% CI [−0.15, 0.44], $t = 0.97$, $p = .661$).

RSA reactivity and resting RSA. We assessed RSA using Electrocardiogram (ECG) recordings according to accepted guidelines (Berntson et al., 1997). RSA was collected during the social stressor task and at rest. For resting RSA, participants were instructed to sit quietly without moving for 3 min. We used a modified Lead II configuration, with electrodes on the left and right clavicle and left lower torso. ECG and respiration data were sampled at 1.0 kHz using Biopac MP150, ECG/RSP BioNomadix, and Acknowledge (Biopac Systems, Goleta, CA). Trained raters visually inspected automatic R-peak detection of the ECG data using Mindware Heart Rate Variability (HRV) Software (Mindware Technologies, Gahanna, OH). Visual inspection detected ectopic beats and confirmed accurate R-peaks in the ECG waveform. From the IBI time series, we calculated RSA in 1-min bins. To calculate RSA, the HRV module detrended the data using a first-order polynomial to remove the mean and any linear trends, cosine tapered the data, submitted it to Fast Fourier Transformation, and took the natural log integral of high-frequency power (0.10-0.50 Hz). RSA during the social stressor task was calculated as the mean of the five 1-min bins measured during the

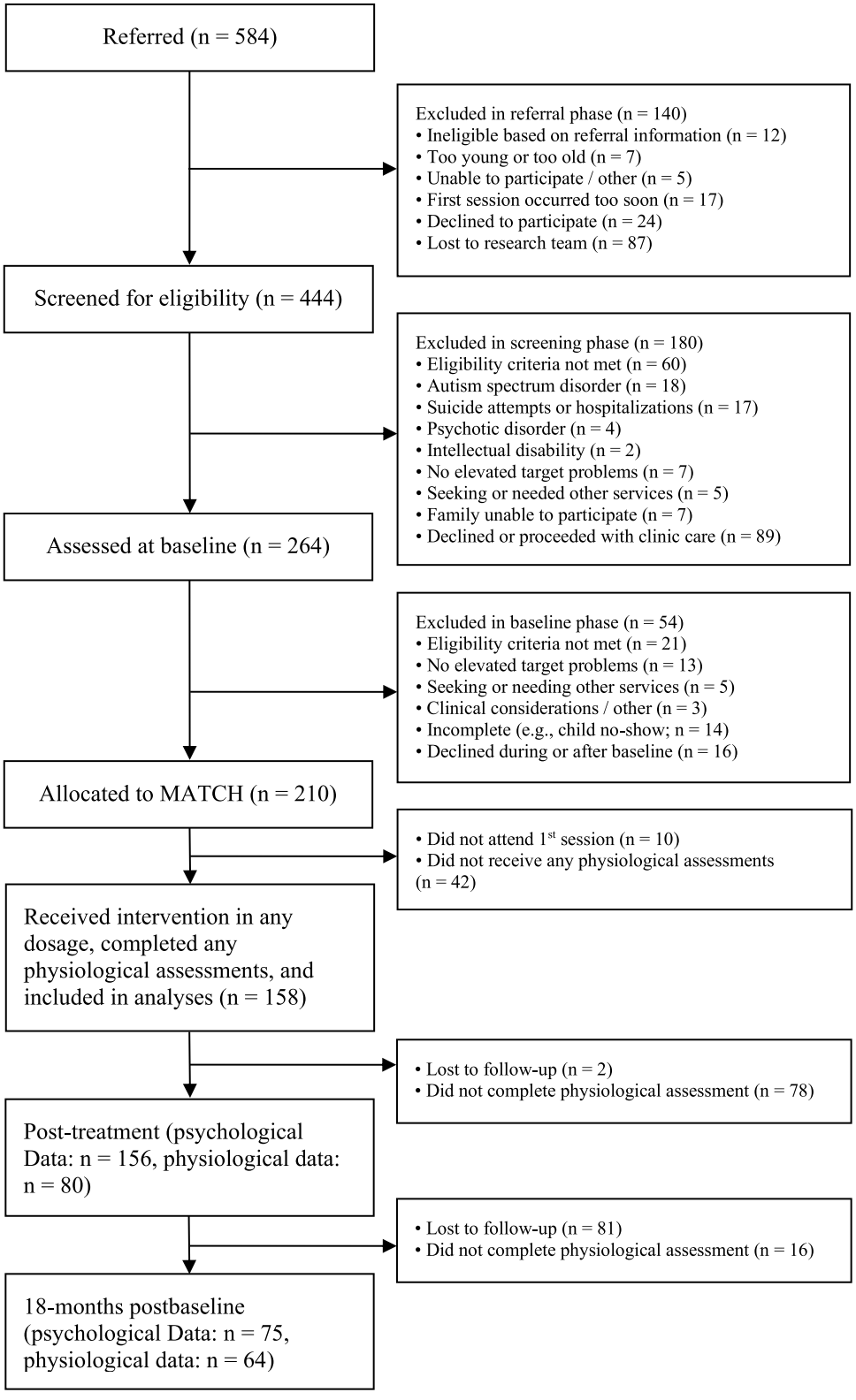

Figure 1. TREND Flow Diagram for participating families.
Note: MATCH = Modular Approach to Therapy for Children.

task. Resting RSA was calculated as the mean of the three 1-min bins at rest. RSA reactivity was calculated as the difference between resting RSA and RSA during the social stressor task (i.e., RSA reactivity = resting RSA – task RSA), such that high values indicate reduced RSA relative to RSA at rest.

Table I. Participant characteristics.

	%	*N*
Assigned Female Biological Sex Birth	48.1	76
Race/Ethnicity		
Asian	1.3	2
Black	28.5	45
Hispanic/Latine	20.9	33
White	35.4	56
Multiracial	12.7	20
Other	1.3	2
Family Income		
$0–$19,000	34.2	54
$20,000–$39,000	27.2	43
$40,000–$59,000	15.2	24
$60,000–$99,000	13.9	22
$100,000 or more	5.0	8
Psychiatric Medication (yes)	20.9	33
Received Learning to Relax Module	22.2	35
Received Quick Calming Module	20.8	33
Received Either Module	27.8	44
Received Both Modules	15.2	24
Primary Problem/MATCH Protocol:		
Anxiety	22.0	35
Depression	39.0	62
Trauma	1.3	2
Conduct	37.7	60
% of Total Sessions for Recipients of:	%	***SD***
Learning to Relax	9.7	11.3
Quick Calming Module	7.6	7.3
Either Module	17.2	13.3

	Baseline				**Post-Treatment**				**18Mo**			
	M	***SD***	***Min***	***Max***	***M***	***SD***	***Min***	***Max***	***M***	***SD***	***Min***	***Max***
Age	10.7	2.5	7.0	15	–	–	–	–	–	–	–	–
Internalizing	65.2	8.8	41.0	79	56.0	10.8	33	80	51.3	12.1	33	80.
Externalizing	64.6	9.0	34.0	80	57.5	11.3	33	86	54.1	11.9	33	80
Resting RSA	6.5	1.2	1.7	8.6	6.9	1.3	3.0	9.6	7.1	1.6	3.4	14.3
RSA Reactivity	0.5	0.9	−2.1	2.9	−0.1	1.1	−3.4	2.1	0.1	1.2	−2.3	4.4
Speech RSA	5.9	1.1	0.2	8.6	7.0	1.1	4.7	10.2	7.0	1.1	3.4	9.9
MATCH Sessions	–	–	–	–	10.8	9.3	1	47	–	–	–	–

Therapy Modules Containing Slow-breathing Content

At the end of each therapy session, study therapists recorded which modules they covered during that therapy session. There were 33 modules therapists could choose from, and the order of modules administered was based primarily on one's protocol selection (Anxiety, Depression, Trauma, or Conduct) and on changes during treatment and clinical judgment. For this study, we examined whether the Quick Calming or Learning to Relax modules (or Quick Calming and Learning to Relax combined) were administered at any point during the treatment (i.e., yes/no categorical variable of Quick Calming, Learning to Relax, and whether *either* module was administered at all, respectively). We also examined the dosage of Quick Calming and Learning to Relax during treatment (i.e., continuous count of how many sessions the Quick Calming, Learning to Relax, and the combined modules were respectively covered). Both modules include slow breathing, relaxing muscles, and calming imagery. Quick calming emphasizes slow breathing and practice in the context of stressful situations. Learning to relax emphasizes deep muscle relaxation, calming imagery, and practice at home in a quiet setting.

Data Analysis

We preregistered analyses, and the analysis code is publicly available (osf.io/7jgp8/). We conducted analyses in R Version 4.1.2. All analyses included the child's baseline age, sex, and number of MATCH sessions attended as covariates. Analyses without internalizing or externalizing symptoms as the dependent variable included both as covariates. Analyses with RSA reactivity as the dependent variable included

resting RSA as a covariate. We used multilevel modeling, with restricted maximum likelihood estimation and the assumption of data missing at random. Multilevel models provide unbiased estimates in the presence of missing data (Rabe-Hesketh & Skrondal, 2008). Outcome variables (i.e., RSA reactivity, resting RSA, internalizing symptoms, externalizing symptoms) were modeled as continuous variables.

We modeled time as a fixed effect using a categorical variable for timepoint (0 = pre-treatment, 1 = post-treatment, 2 = 18-months postbaseline), with pre-treatment as the reference. We used a categorical variable for timepoint rather than time as a continuous variable for several reasons. First, linear slopes are not appropriate because change in MATCH has been shown to be non-linear, with improvement being faster pre to post and slower at follow-ups (Chorpita et al., 2013; Weisz et al., 2020). If we modeled time as a nonlinear (e.g., logarithmic) term, this would assume the rate of nonlinear change is equivalent during treatment as compared to after treatment. Modeling timepoint as a categorical variable relaxes this assumption (Rabe-Hesketh & Skrondal, 2008). This approach is appropriate for our three-occasion data and notably anchors time to clinically meaningful occasions for each youth (i.e., baseline, post, and follow-up), which could vary in their timing given that the treatment period was not fixed. Given this variability in dosage/duration of treatment, we included the number of sessions attended (an index of treatment dosage) as a covariate. We included a subject-specific random intercept and used the Benjamini-Hochberg correction for multiple testing (Benjamini & Hochberg, 1995). Analyses used the intention-to-treat population, and we report standardized effect sizes for all analyses.

For Aim 1, we estimated multi-level models to determine whether RSA reactivity increased from pre to post and pre to 18Mo. We conducted post-hoc analyses examining whether resting RSA increased from pre to post and from pre to 18Mo to further understand the unexpected findings from Aim 1 (described further in Discussion). For Aim 2, multi-level models estimated whether increases in RSA reactivity predicted reductions in internalizing or externalizing symptoms. We conducted post-hoc analyses examining whether changes in resting RSA predicted reductions in internalizing or externalizing symptoms. These models included predictors for timepoint (i.e., pre, post, or 18Mo), RSA reactivity or resting RSA, and a subject-specific mean of RSA reactivity or resting RSA, respectively.

To further understand our findings, we also conducted post-hoc analyses exploring whether RSA reactivity and resting RSA interacted to predict internalizing and externalizing symptoms. Empirical precedent supported the possibility of this interaction effect (Hinnant & El-Sheikh, 2013; Yaroslavsky et al., 2013). We included predictors for resting RSA, RSA reactivity, their interaction term, timepoint, and a subject-specific mean of RSA reactivity and resting RSA in predicting internalizing or externalizing symptoms. We conducted a generalized variance inflation factor (GVIF) analysis to evaluate the variables in these models for multicollinearity (Fox & Monette, 1992). In these models, no variable had a $GVIF^{1/2*Df}$ score above two, which is a conservative threshold for inferring multicollinearity (Fox & Monette, 1992).

We examined our pre-registered exploratory aims using similar modeling strategies. To explore whether changes in RSA reactivity or in resting RSA interacted with administration of either of the modules (i.e., Quick Calming and Learning to Relax) with slow-breathing exercises, we estimated models with timepoint, coverage of these modules in therapy (categorical, as covered yes/no; continuous, as number of sessions administered), and their interaction in predicting change in RSA reactivity or in resting RSA (see Supplementary Materials, Table S3 for results of both modules combined). To investigate whether pre-treatment RSA reactivity or resting RSA predicted symptom change, we estimated models with timepoint, baseline RSA reactivity, or baseline resting RSA and their interaction in predicting change in internalizing and externalizing psychopathology. We also conducted pre-registered sensitivity analyses that included psychiatric medication status (categorical, yes/no) as a covariate. Descriptive information of participants by internalizing vs. externalizing protocol can be found in Table S4.

Results

Descriptive Statistics and Preliminary Analyses

Demographic and descriptive statistics for all primary variables are in Table I. The number of MATCH sessions and module dosage were determined by youths and therapists. However, neither resting RSA ($\beta = -0.03$, 95% CI [−0.23, 0.15], $p = .683$), RSA reactivity ($\beta = 0.03$, 95% CI [−0.16, 0.22], $p = .726$), internalizing ($\beta = 0.11$, 95% CI [−0.06, 0.28], $p = .205$), nor externalizing problems ($\beta = -0.13$, 95% CI [−0.30, 0.04], $p = .139$) at pre-treatment predicted the number of MATCH sessions. Also, neither resting RSA nor RSA reactivity predicted the dosage of the Quick Calming (resting RSA: $\beta = -0.12$, 95% CI [−0.30, 0.06], $p = .192$; RSA reactivity: $\beta = 0.03$, 95% CI [−0.15, 0.21], $p = .724$), and Learning to Relax modules (resting RSA: $\beta = -0.14$, 95% CI [−0.33, 0.05], $p = .152$; RSA reactivity: $\beta = 0.10$, 95% CI [−0.09, 0.30], $p = .309$). Results of analyses for aims 1-2, exploratory (expl.) aims 1-2, and post-hoc analyses 1–3 are in Table II.

Table II. Results of multi-level modeling analyses for study aims.

Changes in RSA reactivity (Aim 1)			
	β	95% CI	Corrected *p*-value
Pre-Post	–0.80	[–1.04, –0.56]	**<.001**
Pre-18Mo	–0.64	[–0.89, –0.39]	**<.001**
Changes in resting RSA (Post-hoc 1)			
	β	95% CI[a]	Corrected *p*-value
Pre-Post	0.22	[0.00, 0.45]	**.049**
Pre-18Mo	0.45	[0.20, 0.69]	**< .001**
Changes in RSA reactivity predicting psychopathology (Aim 2)			
	β	95% CI	Corrected *p*-value
Internalizing	0.03	[–0.09, 0.14]	.635
Externalizing	–0.02	[–0.12, 0.07]	.602
Changes in resting RSA predicting psychopathology (Post-hoc 2)			
	β	95% CI	Corrected *p*-value
Internalizing	0.03	[–0.09, 0.15]	.643
Externalizing	0.05	[–0.05, 0.15]	.346
Do resting RSA and RSA reactivity interact to predict symptom change? (Post-hoc 3)			
	β	95% CI	Corrected *p*-value
Internalizing	–0.08	[0.01, 0.14]	**.024**
Externalizing	–0.07	[0.01, 0.13]	**.014**
Modules with slow-breathing exercises predicting change in RSA reactivity (Expl. Aim 1)			
	β	95% CI	Corrected *p*-value
Learning to relax dosage.			
Pre-Post	–0.01	[–0.31, 0.30]	.972
Pre-18Mo	–0.16	[–0.42, 0.11]	.247
Quick calming dosage.			
Pre-Post	–0.11	[–0.35, 0.12]	.346
Pre-18Mo	–0.36	[–0.60, –0.12]	**.008**
Learning to relax (yes/no).			
Pre-Post	0.03	[–0.22, 0.28]	.812
Pre-18Mo	–0.10	[–0.34, 0.14]	.812
Quick calming (yes/no).			
Pre-Post	–0.08	[–0.32, 0.16]	.505
Pre-18Mo	–0.38	[–0.62, –0.14]	**.005**
Modules with slow-breathing exercises predicting change in resting RSA (Expl. Aim 1)			
	β	95% CI	Corrected *p*-value
Learning to relax dosage.			
Pre-Post	0.17	[–0.06, 0.41]	.150
Pre-18Mo	0.21	[–0.04, 0.46]	.150
Quick calming dosage.			
Pre-Post	0.17	[–0.04, 0.38]	.110
Pre-18Mo	0.48	[0.25, 0.70]	**<.001**
Learning to relax (yes/no).			
Pre-Post	0.22	[–0.01, 0.44]	.114
Pre-18Mo	0.11	[–0.13, 0.35]	.352
Quick calming (yes/no).			
Pre-Post	0.16	[–0.07, 0.38]	.165
Pre-18Mo	0.20	[–0.05, 0.44]	.165
Resting RSA or RSA reactivity and treatment response (Expl. Aim 2 & Post-hoc 4)			
	β	95% CI	Corrected *p*-value
Pre-treatment RSA reactivity			
Internalizing Pre-Post	0.01	[–0.13, 0.15]	.874
Internalizing Pre-18Mo	–0.20	[–0.37, –0.02]	*.055*
Externalizing Pre-Post	–0.02	[–0.14, 0.10]	.756
Externalizing Pre-18Mo	–0.15	[–0.30, 0.01]	.135

Pre-treatment resting RSA (Post-hoc)			
Internalizing Pre-Post	–0.04	[–0.19, 0.09]	.513
Internalizing Pre-18Mo	–0.16	[–0.33, 0.02]	.146
Externalizing Pre-Post	–0.14	[–0.27, –0.01]	**.032**
Externalizing Pre-18Mo	–0.21	[–0.37, –0.06]	**.015**

Note. Pre-Post refers to pre-treatment to post-treatment change; Pre-18Mo refers to pre-treatment to 18-months postbaseline change. β = Standardized effect size. Bolded values denote significance ($p < 0.05$). We included child's baseline age, sex, and number of MATCH sessions attended as covariates. Analyses that did not have internalizing or externalizing symptoms as dependent variables included both as covariates. Analyses with RSA reactivity as the dependent variable included baseline resting RSA as a covariate. Analyses probing the association between change in RSA reactivity or resting RSA, or their interaction, with change in symptoms included a subject-specific mean of RSA reactivity, resting RSA, or both, respectively.

Changes in RSA Reactivity and Resting RSA (Aim 1 and Post-hoc 1)

As seen in Table II (top), RSA reactivity decreased pre- to post-treatment (pre to post) ($\beta = -0.80$, $p < .001$) and pre- to 18-months postbaseline (pre to 18Mo) ($\beta = -0.64$, $p < .001$). In post-hoc analyses, resting RSA increased pre to post ($\beta = 0.22$, $p = .049$) and pre to 18Mo ($\beta = 0.45$, $p < .001$).

Changes in Resting RSA or RSA Reactivity Predicting Psychopathology (Aim 2 & Post-hoc 2)

Changes in RSA reactivity did not predict changes in internalizing or externalizing symptoms (ps = .602 to .635). In post-hoc analyses, changes in resting RSA did not predict changes in internalizing symptoms or externalizing symptoms (ps = .346 to .643).

Do Resting RSA and RSA Reactivity Interact to Predict Symptom Change? (Post-hoc 3)

In post-hoc analyses, we found two significant interactions between RSA reactivity change and resting RSA change in predicting change in internalizing ($\beta = -0.08$, $p = .024$) and externalizing ($\beta = -0.07$, $p = .014$) symptoms over time. A visualization of these interaction effects is provided in Figure 2. As shown (see Figure 2, left sides of Panels A and B), for participants who showed greater decreases (or more negative change) in their RSA reactivity over time, increases in their resting RSA were associated with reductions in both internalizing and externalizing symptoms. At the same time, for participants who showed greater increases (or more positive change) in their RSA reactivity over time (see right side of Figure 2), increases in their resting RSA predicted increases in their internalizing and externalizing symptoms.

Modules with Slow-Breathing Exercises Predicting Change in RSA Reactivity (Expl. Aim 1)

As seen in Table II (middle), dosage of Learning to Relax did not predict pre to post or pre to 18Mo changes in RSA reactivity (ps = .247 to .972). Whether Learning to Relax was covered did not predict changes in RSA reactivity pre to post or pre to 18Mo (ps = .812). Quick Calming dosage did not predict changes in RSA reactivity pre to post ($p = .346$) but predicted greater decreases pre to 18Mo ($\beta = -0.36$, $p = .008$). Whether Quick Calming was covered did not predict changes in RSA reactivity pre to post ($p = .505$) but predicted greater decreases pre to 18Mo ($\beta = -0.38$, $p = .005$).

Modules with Slow-Breathing Exercises Predicting Change in Resting RSA (Expl. Aim 1)

Dosage of Learning to Relax did not predict increases in resting RSA pre to post or pre to 18Mo (ps = .150). Whether Learning to Relax was covered did not predict changes in resting RSA pre to post or pre to 18Mo (ps = .114 to .352). A higher Quick Calming dosage did not predict greater increases in resting RSA pre to post ($p = .110$) but did predict greater increases in resting RSA pre to 18Mo ($\beta = 0.48$, $p < .001$). Whether the Quick Calming module was administered was not associated with changes in resting RSA pre to post or pre to 18Mo (ps = .165).

Resting RSA or RSA Reactivity and Treatment Response (Expl. Aim 2 and Post-hoc 4)

In pre-registered exploratory analyses, as shown in Table II (bottom), pre-treatment RSA reactivity did not predict pre to post changes in internalizing symptoms or externalizing symptoms (ps = .756 to .874). Higher pre-treatment RSA reactivity did not predict greater pre to 18Mo decreases in internalizing symptoms (ps = .055 to .135) or externalizing symptoms. In post-hoc analyses, pre-treatment resting RSA did not predict changes in internalizing symptoms pre to post (ps = .146 to .513) or pre to 18Mo. However, pre-treatment resting RSA predicted changes in externalizing symptoms pre to post ($\beta = -0.14$, $p = .032$) and pre to 18Mo ($\beta = -0.21$, $p = .016$).

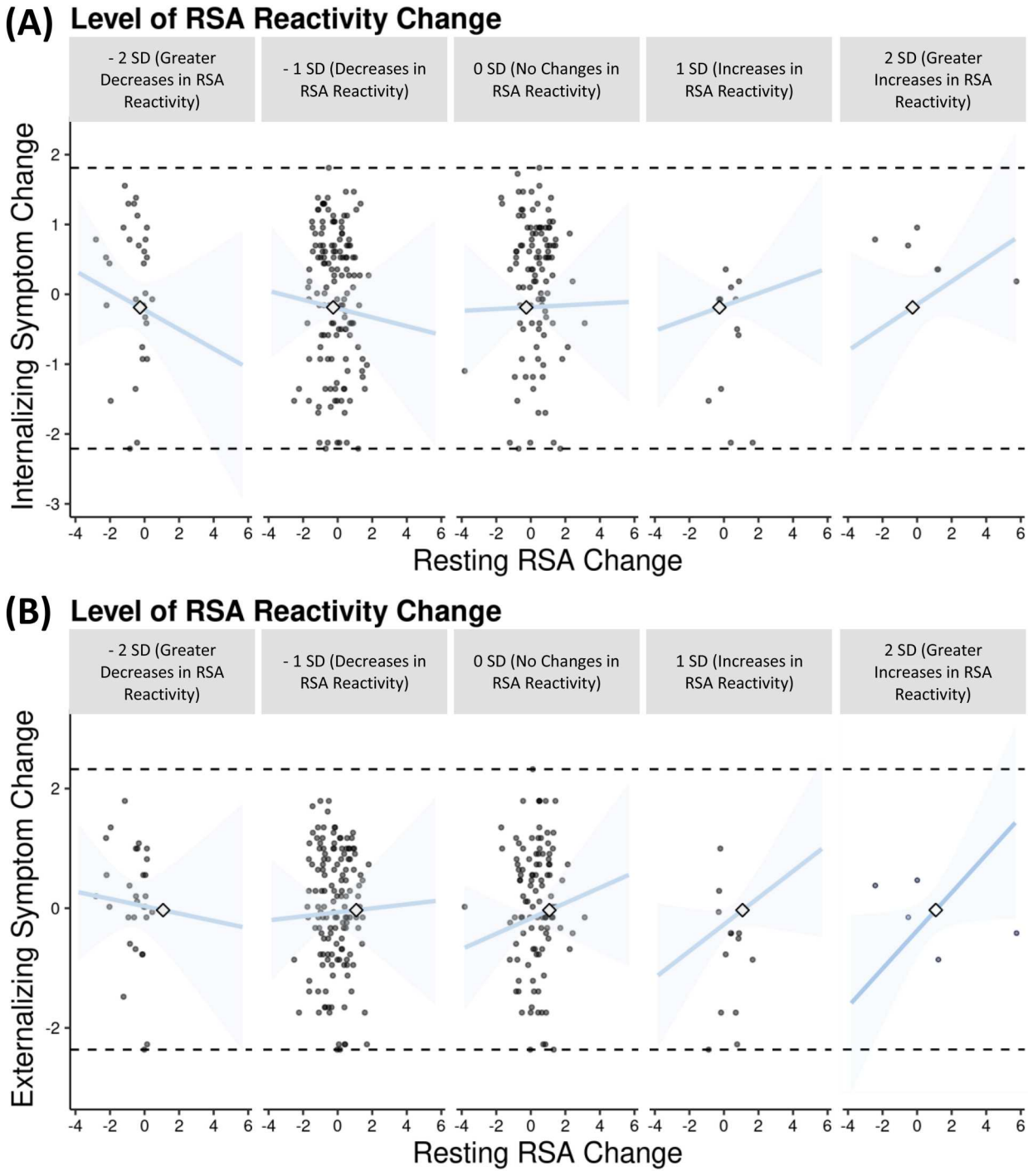

Figure 2. Decreased RSA reactivity combined with increased resting RSA predicted reduced internalizing and externalizing symptoms (Post-hoc Analysis 3).
Note: (A) The association between changes in resting respiratory sinus arrhythmia (RSA) and changes in internalizing symptoms at different levels of RSA reactivity change. (B) The association between changes in resting respiratory sinus arrhythmia (RSA) and changes in externalizing symptoms at different levels of RSA reactivity change.

Sensitivity Analyses

Results did not change when covarying for psychiatric medication status (see Supplementary Materials, Table S5). In post-hoc sensitivity analyses, the pattern of results for the exploratory analyses of the modules containing slow-breathing did not change when covarying for youths' assigned MATCH protocol (Anxiety, Depression, Trauma Conduct).

Discussion

We aimed to take the first step in clarifying whether resting RSA and RSA reactivity change in the context of CBT and whether such changes, in turn, predict reduced psychopathology. We found that RSA reactivity (surprisingly) decreased and, in post-hoc analyses, resting RSA increased pre to post and pre to 18Mo. These findings raise the possibility that RSA reactivity and resting RSA are modifiable in the context of transdiagnostic, modular youth CBT. Changes in RSA reactivity and resting RSA, in isolation, did not predict changes in psychopathology. However, post-hoc analyses revealed an interaction: decreases in RSA reactivity combined with increases in resting RSA predicted reductions in psychopathology, raising the possibility that the changes observed in RSA reactivity and resting RSA were a positive outcome because they predicted a reduction in symptoms of psychopathology following treatment. In pre-registered exploratory analyses, dosage of the Quick Calming module, which includes slow-breathing exercises, predicted greater decreases in RSA reactivity and greater increases in resting RSA pre to 18Mo. Although experimental studies are needed, this raises the possibility that slow breathing may be a method for fostering lasting changes in RSA reactivity and resting RSA in youth.

The first aim examined whether there were increases in RSA reactivity in the context of CBT. RSA reactivity decreased pre to post and pre to 18Mo— the opposite direction of what we expected. Although findings on the association between RSA reactivity and psychopathology are somewhat mixed (Graziano & Derefinko, 2013), growing evidence seems to suggest that high RSA reactivity in the context of low resting RSA is positively associated with psychopathology (Hinnant & El-Sheikh, 2013; Yaroslavsky et al., 2013). Given post-hoc analyses showing increases in resting RSA pre to post and pre to 18Mo, we conducted further analyses examining if this pattern of reduced RSA reactivity and increased resting RSA predicted reduced psychopathology. Indeed, decreases in RSA reactivity more strongly predicted symptom reduction among those with greater increases in resting RSA. We did not examine whether participants who exhibited this pattern of changes were better able to cope with potential short-term stress/anxiety evoked by the task. However, the findings suggest that decreases in RSA reactivity could be adaptive in the long-term in the context of increased resting RSA during CBT because they predicted reduced symptoms of psychopathology following treatment, which was assessed through 18-month follow-up. Still, given that these analyses were post-hoc, more work is needed to clarify the interaction between resting RSA and RSA reactivity in relation to psychopathology. Given that high resting RSA tends to be negatively associated with psychopathology even in isolation (Hinnant & El-Sheikh, 2013), increases in resting RSA may be considered a positive outcome. This is the first study to our knowledge to show changes in RSA reactivity and resting RSA over an 18-month period in youth who received EBPT. These findings could reflect heightened malleability or the natural time course of the two processes, but both RSA reactivity and resting RSA have been shown to remain relatively unchanged during the period of development spanned by the study sample (ages 7–15; Dollar et al., 2020). So, the findings raise the possibility that RSA reactivity and resting RSA are modifiable in the context of CBT (e.g., MATCH). An empirically sound test of this notion in the future will require a design in which youth are randomly assigned to a specified treatment or a control/comparison group.

The second aim examined whether greater increases in RSA reactivity predicted greater decreases in internalizing and externalizing symptoms. Changes in RSA reactivity did not predict decreases in internalizing and externalizing symptoms. In post-hoc analyses, changes in resting RSA also did not predict decreases in internalizing and externalizing symptoms. Although these findings do not support RSA reactivity and resting RSA, on their own, as contributors to the amelioration of psychopathology, post-hoc analyses raise the possibility that decreases in RSA reactivity in the context of increases in resting RSA may predict reductions in psychopathology in youth. Moreover, the protective effects of RSA reactivity and resting RSA may be most pronounced among those exposed to trauma and adversity (McLaughlin et al., 2014; Susman et al., 2021). Although the pattern of results regarding the modules containing slow breathing did not change when controlling for MATCH protocol (Anxiety, Depression, Conduct, Trauma), only two out of 158 youth in this study were assigned the Trauma protocol. Future research with greater representation of youth exposed to trauma is needed to further clarify the associations of RSA reactivity and resting RSA with psychopathology in youth psychotherapy.

Pre-registered exploratory analyses examined if changes in RSA reactivity and resting RSA were predicted by whether the modules with slow-breathing exercises (e.g., Quick Calming) were covered in therapy or their dosage. Higher dosage of Quick Calming predicted more decreases in RSA reactivity and more increases in resting RSA. Quick Calming administration (yes/no) predicted greater decreases in RSA reactivity from pre to 18Mo. Although Quick Calming-related changes in RSA were not

observed at post-treatment, it's possible that it may take longer than the duration of treatment for the potential effects of the modules containing slow-breathing exercises or their practice in daily life to fully manifest biologically. There were significant associations between changes in RSA reactivity, but not resting RSA, and whether either module containing slow-breathing exercises was administered or not. These findings raise the question of whether other treatment components may account for changes in resting RSA. However, it's also possible that minimal coverage of slow-breathing techniques may be sufficient to influence RSA reactivity, whereas repeated practice of slow-breathing may be needed for the vagus nerve to become sufficiently "toned" over time such that increases can be observed at rest.

The Learning to Relax module did not predict resting RSA or RSA reactivity. Interestingly, the MATCH treatment manual seems to more frequently emphasize slow breathing in the Quick Calming module relative to the Learning to Relax module (Chorpita & Weisz, 2009). Learning to Relax places a more central focus on progressive muscle relaxation and guided imagery compared to slow breathing (Chorpita & Weisz, 2009). This appears consistent with our findings of no significant effects of Learning to Relax relative to a considerable number of significant effects of Quick Calming on RSA reactivity and resting RSA. One might expect Quick Calming and Learning to Relax to be administered for similar problems, but only Quick Calming predicted changes in RSA—the module that places greater emphasis on slow breathing. This raises the possibility that repeated practice of slow-breathing exercises can lead to long-term increases in resting RSA and decreases in RSA reactivity in youth.

That said, this possibility should be advanced cautiously for at least four reasons. First, Quick Calming differs from Learning to Relax in ways other than the use of slow breathing; for example, Quick Calming is intended for immediate use in situations where uncomfortable arousal surfaces and needs to be addressed immediately (e.g., just before a sports event or a presentation in front of one's class), so it is possible that immediate access to self-regulation is especially relevant to RSA reactivity and resting RSA. Second, there are 33 modules in MATCH and a massive number of possible combinations and possible sequences (Chorpita & Weisz, 2009). The lag between module use and its impact remains unknown, and of course, that lag may differ for different modules and different youths. Third, the modules were not assigned randomly. They were based primarily on initial clinical assessment, which dictated one's protocol selection, and secondarily on changes during treatment and clinical judgment, so any symptom change that follows a module could be partly an effect of what had happened prior to the module. Fourth, the Quick Calming and Learning to Relax modules were not specifically indicated in the Externalizing protocol unless there were overlapping Internalizing symptoms. Although we covaried baseline internalizing and externalizing symptoms in our analyses, randomized controlled trials are needed to clarify the effects of slow breathing, immediate self-regulation, and other aspects of the Quick Calming module on RSA reactivity and resting RSA.

The second exploratory aim was to examine whether pre-treatment RSA reactivity predicted reductions in externalizing and internalizing symptoms. Pre-treatment RSA reactivity did not predict greater symptom reduction pre to 18Mo. However, in post-hoc analyses, high pre-treatment resting RSA predicted greater reductions in externalizing (but not internalizing) symptoms. These results contradict findings that fourth-grade children with low RSA are more likely to respond to psychotherapy than those with high RSA (Glenn et al., 2019). We cannot discount the possibility that high resting RSA may just predict adaptive outcomes (i.e., lower externalizing symptoms) over time, as has been shown longitudinally without treatment (Susman et al., 2021). That said, it is possible that during most of the developmental period spanned by the study sample (ages 7-15), youth with high resting RSA may be more able to develop a therapeutic alliance, sit with challenging emotions during sessions, and/or more quickly uptake adaptive emotion regulation strategies, and thus benefit more from treatment (Kok & Fredrickson, 2010).

This study has several limitations. First, although this study contributes to the literature by examining changes in RSA in the context of psychological treatment up until 18 months postbaseline, longer follow-ups tend to incur greater attrition (Karlson & Rapoff, 2009). Indeed, the level of missing physiological data at post-treatment (49.4%) and at 18-month postbaseline (59.5%) could have led to bias in the findings. Replication is needed to gain certainty that these findings were not due to attrition bias. RSA was collected by peripatetic research associates in community settings; although this may contribute to greater ecological validity, this may have contributed to noise in the RSA measures. Resting RSA was recorded over a 3-min period rather than 5 min like for speech RSA due to time constraints. Although baseline periods $\geq$1 min are considered to be a minimum duration for reliable RSA quantification according to accepted guidelines (Berntson et al., 1997), and many studies have collected resting RSA for $\leq$ 3 min and/or different durations from speech RSA (Beauchaine et al., 2019), it is unclear whether the different durations would have any

impact on the findings. Although respiration was accounted for in our analysis, and this is thought to provide a purer index of parasympathetic activity, we cannot rule out the possibility that sympathetic activity could have also influenced RSA to some extent (Berntson et al., 1997; Thayer et al., 2012). Also, some evidence suggests there are racial differences in resting RSA, but not RSA reactivity, in youth, and current models of resting RSA for White youth may not apply to youth of color (Dollar et al., 2020). Although our sample was racially diverse, future research is needed to understand the specific effects of race on models of resting RSA in the context of psychotherapy. The particular form of CBT used in this study was the transdiagnostic, modular MATCH program (Chorpita & Weisz, 2009); whether the findings apply to other forms of CBT is a question for future research. Finally, several analyses, as noted, were post-hoc and should be considered preliminary until replicated.

Other factors could have played a role in changing RSA reactivity and resting RSA. For example, given the integral role the vagus nerve is thought to play in social functioning (Kok & Fredrickson, 2010), the therapeutic alliance could contribute to toning the vagus nerve over the course of psychotherapy. Therapy could have boosted physical activity, leading to better cardiorespiratory health that could have contributed to the findings (Grossman & Taylor, 2007). In this real-world effectiveness trial, some youth may have received other psychological services between post and 18 months. A third of clients received other services at 1 and 2 years postbaseline in previous research with MATCH (Chorpita et al., 2013; Weisz et al., 2012), yet treatment gains in MATCH were superior to usual care at one year and maintained at two years postbaseline, even while youth in MATCH had the lowest utilization of other services at 1-year postbaseline and similar utilization at 2-years postbaseline. This suggests that the differences in psychological outcomes were unlikely to be influenced by differences in additional service utilization. Also, although there was variability in the number of MATCH treatment sessions that youth received, we controlled for MATCH dosage in all analyses, so it is unlikely that outcomes are being driven by dosage of treatment. It's always possible that decreases in RSA reactivity during the Modified Trier Social Stress Test for Children (TSST-C) could have resulted from habituation over repeated exposures. However, RSA reactivity has been shown to remain stable (i.e., without habituation) across repeated exposures to the TSST-C (Boesch et al., 2014; Maier et al., 2022). Moreover, greater intervals between assessments appear to reduce the risk of habituation (Allen et al., 2014), and habituation would not explain why Quick Calming predicted greater changes in RSA. Thus, it seems unlikely that decreases in RSA reactivity were a result of habituation to repeated exposures or exposure therapy. Indeed, the pattern of results regarding the Quick Calming Module did not change when covarying for MATCH protocol (Anxiety, Depression, Conduct, Trauma), so it appears that the changes in RSA predicted by the Quick Calming module were not explained by the variation in other protocol-specific elements. This study did not include a randomly assigned non-MATCH condition, so we cannot rule out a possible effect of time on RSA. Although RSA reactivity and resting RSA have shown to remain stable across time over the age range spanned by the study sample (Dollar et al., 2020), a randomized controlled trial involving a treatment-control comparison is needed to ensure that changes in RSA reactivity and resting RSA are not due to other factors and to isolate the active ingredients to confer these lasting changes. Only two youths (1.9%) reported medical conditions known to the authors to influence RSA (i.e., epilepsy and sickle cell, see Table S6), and thus appear unlikely to affect the overall findings (Chalacheva et al., 2015; Fisher et al., 2022). Asthma does not appear to influence RSA (Lehrer et al., 1994).

To our knowledge, there is limited research on change in RSA reactivity and resting RSA in the context of youth EBPTs. The results extend the literature showing that RSA reactivity and resting RSA tend not to change across development from ages 8 to 15 by showing that lasting, potentially adaptive changes might be possible with psychological intervention—yet more studies are needed to be sure. Although changes in RSA reactivity and resting RSA did not predict reduced psychopathology in isolation, the observed combination of decreases in RSA reactivity and increases in resting RSA predicted reduced psychopathology in youth. Also, many studies have shown slow breathing to temporarily increase resting RSA in lab settings or in adults. This study raises the possibility that slow-breathing exercises may be a path for creating lasting changes in RSA reactivity and, perhaps when covered more frequently in therapy, resting RSA in youth. Given that the analyses of the modules containing slow-breathing exercises were exploratory, future research is needed to further understand the effects of slow-breathing practice on RSA. Moreover, high resting RSA could serve as a potential biomarker of treatment response, which will be important for future studies to replicate. Future research should investigate resting RSA in combination with RSA reactivity as a possible transdiagnostic process. Findings raise the possibility that resting RSA and RSA reactivity could be

modifiable predictors of symptom change in CBT that contribute to the amelioration of psychopathology in youth.

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Disclosure Statement

At the time of writing this manuscript, Eli Susman was a scientific advisor for Chorus Wellness Inc. and received compensation for his time. However, he is no longer affiliated with Chorus Wellness Inc. His role was to ensure the quality of Chorus's science, and he never received financial incentives (e.g., stocks) tied to the company's success. John Weisz is a co-author of the treatment manual used in this study (i.e., MATCH); he receives royalties for its sales and research funding from the NIMH (R01MH124965), the Institute of Education Sciences (R305A140253), the Manton Foundation, the Marriott Foundation, and School Mental Health Ontario. The other authors report no conflicts of interest related to this study.

Supplemental data

Supplemental data for this article can be accessed https://doi.org/10.1080/10503307.2024.2308149

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