Respiratory Sinus Arrhythmia – Common and distinct mechanisms of emotional adjustment in the mood and anxiety disorders spectrum?

Dirk Adolph¹, Xiao Chi Zhang¹, Tobias Teismann¹, and Jürgen Margraf²

¹Ruhr-Universität Bochum
²Ruhr-Universität Bochum

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Abstract

Here, we assessed resting respiratory sinus arrhythmia (rRSA) and RSA reactivity (ΔRSA) as common and distinct emotion-adjustment mechanisms for affective and anxiety disorders and their treatments. We recruited samples of healthy controls and patients with anxiety and affective disorders, assessed rRSA during baseline and ΔRSA as RSA-change from baseline to viewing emotional films. Patients then underwent disorder-specific Cognitive Behavior Therapy. Although both patient groups exhibited lower rRSA than controls, depression-, but not anxiety-symptomatology was transdiagnostically associated with less rRSA and ΔRSA. Complementing these depression-specific results, better ΔRSA predicted better treatment-outcome in depression, but not anxiety. Our data confirm RSA as a transdiagnostic marker for mood and anxiety, support recent attempts towards transdiagnostic, dimensional classification systems (HiToP, RDoC) and provide evidence for a more robust association of RSA with depression-symptomatology and -treatment. They thus suggest rRSA and ΔRSA as potential markers to assess common and distinct mechanisms associated with depression and anxiety.

Author Statement

D.A.: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Writing - Original Draft
J.M.: Conceptualization, Resources, Methodology, Supervision, Writing – Review & Editing
X.C.Z: Formal Analysis
T.T.: Resources, Writing – Review & Editing

Corresponding Author

Dr. Dirk Adolph
Mental Health Research and Treatment Center
Ruhr University Bochum
Abstract

Here, we assessed resting respiratory sinus arrhythmia (rRSA) and RSA reactivity (ΔRSA) as common and distinct emotion-adjustment mechanisms for affective and anxiety disorders and their treatments. We recruited samples of healthy controls and patients with anxiety and affective disorders, assessed rRSA during baseline and ΔRSA as RSA-change from baseline to viewing emotional films. Patients then underwent disorder-specific Cognitive Behavior Therapy. Although both patient groups exhibited lower rRSA than controls, depression-, but not anxiety-symptomatology was transdiagnostically associated with less rRSA and ΔRSA. Complementing these depression-specific results, better ΔRSA predicted better treatment-outcome in depression, but not anxiety. Our data confirm RSA as a transdiagnostic marker for mood and anxiety, support recent attempts towards transdiagnostic, dimensional classification systems (HiToP, RDoC) and provide evidence for a more robust association of RSA with depression-symptomatology and -treatment. They thus suggest rRSA and ΔRSA as potential markers to assess common and distinct mechanisms associated with depression and anxiety.

Keywords: Respiratory Sinus Arrhythmia, Depression, Anxiety, Prediction of Treatment Outcome, Transdiagnostic Approach

Introduction

Although current nosologic systems list affective and anxiety disorders as distinct disorder categories, they are highly comorbid and share a considerable amount of symptomatology. Consequently, there is still debate on how these disorders are separable in terms of their underlying pathogenic processes. Indeed, while depression and anxiety share a liability towards enhanced negative affectivity, there is also consensus between current models that many anxiety disorders (e.g. panic disorder, specific phobias or PTSD), but not affective disorders, are related to elevated threat responses and physiological hyperarousal. In turn, with some exceptions low positive affect or blunted emotional reactivity towards a broad range of emotional stimuli is related to affective rather than anxiety disorders. Several lines of research so far have focused on identifying objective markers to disentangle these common and distinct emotion-related mechanisms underlying both disorders. Although previous research has argued that within this endeavor, Respiratory Sinus Arrhythmia (RSA) might be a promising candidate, to the best of our knowledge no study to date assessing RSA has included patients from the affective and anxiety disorders spectrum at the same time in one study. The current research aimed at closing this gap. We assessed two common markers of RSA, that is resting RSA (rRSA) and RSA reactivity (ΔRSA), recruited a naturalistic sample of treatment seeking patients with affective and anxiety disorders as well as healthy controls and analyzed the significance these markers have within and across the affective and anxiety disorders as well as the predictive validity both markers have for the outcome of cognitive behavior therapy (CBT).

RSA and psychopathology

RSA is an index of cardiac vagal tone and reflects the activity of a cortico-limbic control system, enabling the flexible regulation of cardiac output via the vagus nerve and the parasympathetic nervous system. RSA is characterized by the variation in heart rate during the breathing cycle. During inhalation, the activity of the vagus nerve is reduced, leading to an increase in heart rate, whereas during exhalation, vagus nerve activity increases, resulting in a decrease in heart rate. Thereby, high levels of rRSA have been previously associated with indices of self-regulation and cognitive control, whereas low rRSA has been associated with measures of cognitive inflexibility. In contrast to rRSA, ΔRSA reflects the momentary change in RSA levels from a
resting state to an emotional or stress-related situation. That is, while at rest, the parasympathetic nervous system acts as a brake, slowing heart rate and promoting homeostasis. When facing significant emotional situations, this “vagal brake” is released (i.e., vagal withdrawal), initiating a decrease in parasympathetic activity and an increase in heart rate to facilitate— in concert with the sympathetic nervous system - an adaptive physiological response to situational demands. Thus, rRSA can roughly be seen as a marker for the organism’s general potential for adaptive physiological responding to emotional or stressful challenges, while ΔRSA reflect the organism’s efficiency in recruiting these reserves in the light of environmental demands. It has been suggested that this healthy adaptation system is impaired in psychopathology, including depression and anxiety, and that both rRSA and ΔRSA might contribute uniquely to between subject variance in psychopathology.

However, despite these theoretical considerations, the literature on the unique role these parasympathetic indices play to differentiate affective and anxiety disorders is contradictory. In detail, confirming general deficits in emotion adaptation and in line with current theoretical models, meta-analytical work has shown that affective and anxiety disorders are associated with low levels of rRSA. In the contrary, while cumulated evidence suggests blunted ΔRSA in depression a recent review did not provide a clear picture of whether anxiety is associated with deviant ΔRSA. Likewise, while there is initial evidence suggesting predictive validity of both rRSA and ΔRSA for depression treatment there is only very limited research on the predictive validity of RSA for treatment outcome in anxiety disorders yielding contradictory results. Taken together, although RSA has been conceptualized as a transdiagnostic biomarker for inflexible emotional responding in psychopathology, research so far does not justify conclusive inferences about the differential effects these vagally mediated processes have within the anxiety and affective disorders spectrum.

The current study

Consequently, within the current study we aimed at closing this gap. We recruited a sample of patients with anxiety and affective disorders, allowing for the evaluation of both unique and shared variance of RSA between anxiety and affective disorders and across the entire anxiety and affective disorders spectrum. We aimed to clarify whether there are interindividual differences in rRSA, as well as ΔRSA based on anxiety and depression psychopathology and whether these two indices are relevant for the outcome of disorder specific cognitive behavioral treatments.

Both research questions were investigated concerning depression and anxiety as distinct diagnostic categories as well as in a transdiagnostic manner across disorder categories. The additional dimensional, transdiagnostic analysis of our data is compatible with the NIMH’s Research Domain Criteria (RDoC) initiative. Traditional classification systems yield limited diagnostic reliability and often fail to account for comorbidity or symptom-heterogeneity, probably as a direct consequence of categorizing dimensional phenomena. Thus, the additional transdiagnostic approach enabled us to consider the contribution of rRSA and ΔRSA as markers of affective self-regulation and cognitive control within and across the anxiety and affective disorders spectrum. Since we aimed for a naturalistic sample of patients attending for treatment at our outpatient center usually yielding high comorbidity rates between depression and anxiety, this approach is especially useful to disentangle the intertwined mechanisms underlying the affective and anxiety disorders spectrum.

Within the current study, we control for a range of methodological issues identified in previous research. In brief, (1) we use negative film clips (i.e. fearful, sad), as well as a happy and neutral film to assess ΔRSA. This approach enables us to test if the ΔRSA response in depression in a direct comparison to anxiety, is either based on global emotion-context insensitivity, which should lead to perturbed ΔRSA towards all emotional film clips, or if reduced ΔRSA is restricted to one or more specific, disorder-relevant films (i.e. sad, happy). (2) We strictly followed guidelines in RSA assessment and data reduction in terms of recommended sampling intervals and sampling rate, (3) we controlled for medication, respiration, gender and age, (4) and we assessed the differential predictive validity rRSA and ΔRSA have for treatment outcome in depression and anxiety. (5) To control for putative overlapping effects of the sympathetic nervous system, we additionally recorded the activity of the sympathetic branch of the autonomous nervous system (i.e. in terms of skin conductance level). We did so, because it has been proposed that inconsistent findings in the literature so
far may be founded at least in part on the consideration of isolated parts of physiological regulation system. Indeed, the two branches of the autonomous nervous system work in concert to promote homeostasis and to adapt the organism to current environmental demands including stressful and/or emotional situations. Thus, to determine specificity of the parasympathetic system, the concurrent assessment of sympathetic activity is advantageous.

Based on previous literature as outlined above, we hypothesize that both anxiety and depression are associated with reduced rRSA in comparison to healthy controls. Furthermore, if RSA is indeed transdiagnostically associated with psychopathology, higher symptom load should be associated with lower rRSA. Based on previous findings we hypothesize that depression is associated with diminished ΔRSA towards the emotion induction and that markers of cardiac vagal control are predictive of treatment outcome for depression. Specifically, following previous literature, we hypothesize that ΔRSA in depression will be either reduced mainly towards the happy and sad film clips or following the emotion context insensitivity hypothesis towards the full range of emotion film clips. Due to inconclusive previous literature, no predictions for the predictive validity of RSA markers for the outcome of CBT for anxiety disorders were possible.

**Methods and Materials**

**Sample Characteristics**

The current experiment was part of a larger study assessing mechanisms of anxiety disorders, depression and their treatments. N = 223 patients from the Mental Health Research and Treatment Center of Bochum University participated. Of these, n = 27 did not qualify for a diagnosis of a depressive or an anxiety disorder and had to be excluded from the study. All participants gave written and informed consent to procedures. The study was conducted in accord with the Declaration of Helsinki and was approved by the local ethics committee of the Faculty of Psychology at Ruhr-University Bochum (Approval Number: Votum046). In addition to the patient sample, a total of n = 60 healthy adults (HC) agreed to participate in the current study. The patients sample comprised of depressed patients (DEP, total n = 103, n = 91 Major Depression, n = 9 Dysthymia, n = 3 other depressive disorder) and patients with an anxiety disorder (ANX, total n = 93, n = 28 social phobia, n = 25 panic disorder/ agoraphobia, n = 14 generalized anxiety disorder, n = 8 obsessive compulsive disorder, n = 8 post traumatic stress disorder, n = 6 specific phobia, n = 4 other anxiety disorder) attending for treatment at the outpatient clinic of the Mental Health Research and Treatment Center (MHRTC) at Ruhr University Bochum. All participants were Caucasian and recruited from the Ruhr Area in Germany. Diagnoses were obtained with standardized semi-structured interviews for DSM-IV disorders by trained and certified postgraduate psychotherapists. The diagnoses obtained with the DIPS show very good interrater-reliability (Kappa between χ = 0.72 and χ = 0.92; Suppinger, et al., 2008; Schneider et al., 1992). Diagnoses of healthy controls were obtained with a brief semi-structured interview for DSM-IV disorders. No control participant had to be excluded due to a current or history of mental disorders. A comprehensive sample description can be found in Table 1.

**Treatments**

The patients received manual-based disorder-specific CBT as routinely carried out in our outpatient center (A list of manuals typically used in our center can be found in section 1 of the Supplementary Online Materials). The CBT treatments comprised of approximately 25 sessions and the number of sessions did not differ between depression and anxiety patients (DEP, M = 25.4, SD = 3.7; ANX, M = 25.9, SD = 2.6, p > .10). Treatments were carried out by therapists as part of their postgraduate training. All therapists had a masters' degree in Psychology and at least 1-year full-time postgraduate CBT training. They were additionally monitored by licensed CBT supervisors within regular supervision sessions (i.e., including discussions about the patient’s current status and the ongoing treatment). However, despite general agreement with published manuals (e.g., exposure-based CBT for anxiety disorders) treatments within routine outpatient care are usually less standardized than in typical randomized controlled trials. All treatments were paid for by the German health care insurance system.

**Assessment of Treatment Outcome**
Pre-post symptom change was assessed with the Depression, Anxiety and Stress Scale. The validity of the DASS-21 for clinical populations and to assess treatment outcome has been demonstrated. It has 21 items with 4-point Likert-scales (0=did not apply to me at all to 3=applied to me most of the time). The three DASS subscales can be summed to a total DASS score covering general distress. This DASS-21 general distress score reached excellent internal consistency (in terms of Cronbach's \(\alpha\), \(\text{CR}\alpha\)) in the current sample, \(\text{CR}\alpha = .937\) (DASS-21 subscales: stress \(\text{CR}\alpha = .890\), depression \(\text{CR}\alpha = .935\), anxiety \(\text{CR}\alpha = .837\)).

and was used to assess treatment outcome in the current study. As recommended for pre-post treatment outcome assessment, a residual change score was calculated from the DASS-21 general distress score in line with published recommendations. The resulting DASS General Distress residual changed score covered the change in symptom load from pre to post treatment with higher scores representing higher post treatment residual symptomatology. This pre-post measure was complemented by a two item global success rating, used routinely at MHRTC to assess treatment outcome at the end of the treatment. It assesses patients perceived goal attainment and treatment satisfaction (6-point scales: Have your expectations concerning this treatment been fulfilled?; range: worse than expected – completely fulfilled my expectations; Overall, how much did the treatment help you?, range: worsen the problem – helped very much); Both items are summed up to a global success score (range 2-12). The Global success rating reached acceptable internal consistency in the current sample, \(\text{CR}\alpha= 0.764\)

Film viewing task

For the current study, two sad, two fearful, two happy, and one neutral film clips which have been shown previously to elicit the respective emotions were used. The full description of the film clips and their validation can be found in section 2 of the Supplementary Online Materials. After a 3-minutes baseline RSA measurement (rRSA) a neutral and one randomly chosen sad, one fearful and one happy clip were presented in random order. Prior to the beginning of film viewing, participants were instructed to keep sitting quietly, to breathe regularly, to passively view the film clips and to concentrate on the emotion they elicit. After viewing each of the four film clips, participants were asked to indicate how intensely they felt each of the six basic emotions while watching the clips (visual analogue scales, 0=I did not feel the emotion at all, 100=I extremely felt the emotion). In addition, patients rated the film clips for valence and arousal (data reported elsewhere). In total, this rating procedure had a duration of approximately 30 seconds. Then a black screen was presented for 30 seconds, resulting in a total inter stimulus interval (ISI) consisting of 1 minute².

Procedure

Appointments with patients signaling willingness to participate were made prior to the beginning of the actual treatment and after the diagnostic session. Upon arrival at the laboratory, participants were seated in a comfortable recliner in a dimly lit room. Prior to the beginning of the task, all participants gave informed consent to procedures and filled in the DASS-21. After that, electrodes were attached and the film viewing paradigm began. As part of a larger project, participants also completed an emotion regulation procedure, a conditioning experiment, and an approach avoidance task (reported elsewhere). Upon ending of the experiment, participants indicated on 10 point scales how demanding and arousing the experiment has been. After the experimental session, patients received treatment-as-usual as routinely provided at our outpatient center. After the treatment, all patients were asked to fill in the Global success rating and the DASS-21 again.

Physiological data assessment and data reduction

A lead II ECG was recorded (sampling rate 1000 Hz, digitization 16 bit, Biopac MP100 amplifier system) using Ag/AgCl electrodes. A ground electrode was attached to the participant’s forehead. Respiration was assessed using two respiration belts placed around the abdomen and the thorax. Additionally, electrodermal activity was recorded from the distal phalanxes of the non-dominants hand middel and index finger. Online, data were notch filtered (50Hz). Offline, ECG data were bandpass filtered (5-35Hz, 24dB/oct), and ectopic heartbeats, as well as measurement artifacts were corrected. After trend-removal, interbeat interval data were processed through an end-tapered Hamming Window and FFT was applied to the data. RSA was
extracted for the baseline period and the film clips as the natural logarithm of mean power within the frequency band between 0.15-0.40 Hz. RSA parametrization was done using Kubios HRV (version, 2.1). Electrodermal and respiration data were lowpass filtered (1Hz, 24 db/oct). Respiration rate was obtained using commercial software. In addition to RSA, mean respiration rate (breaths per minute) and mean electrodermal activity (i.e. mean skin conductance level, μS) were calculated for the baseline period and while watching the four film clips. As part of a larger project, M. corrugator suproricIIi, M. zygomaticus major EMG were also recorded (data reported elsewhere).

**Data Analyses**

**Diagnosis-based and transdiagnostic Individual differences in rRSA**

Diagnosis-based and transdiagnostic analysis of individual differences in rRSA

To test for differences in rRSA between diagnostic groups, an ANOVA with the between subject independent variable *diagnostic group* (i.e. DEP, ANX, HC) was run. rRSA (i.e. RSA during the baseline measure prior to the beginning of film viewing part) was used as dependent variable.

To assess the transdiagnostic relationship between rRSA as well as anxiety, depression and stress symptomatology, simple correlations were run. Afterwards, a stepwise linear regression model with the dependent variable rRSA was computed. DASS-21 subscales showing significant simple correlations with rRSA were entered as independent variables.

Taken together, this analytical approach enabled us to assess common and distinct variance in rRSA explained by depression and anxiety diagnosis and symptomatology.

**Διοικητικά διαφορές και Δημιουργία**

Do the film clips elicit significant RSA reactivity (ΔRSA)?

To assess if viewing the films initiated significant RSA reactivity, we ran an ANOVA with the within subject independent variable episode (i.e. resting baseline, happy, neutral, fearful, sad film clip). We await a significant main effect for episode with significantly larger RSA during the baseline period as compared to the film clips.

**Diagnosis-based and transdiagnostic analyses of individual differences in ΔRSA**

To test for individual differences in ΔRSA towards the films, changed scores were calculated between the resting baseline and the four film clips (i.e. ΔRSA = film clip– baseline).

To assess diagnosis-based differences in ΔRSA, an ANOVA was calculated with the between subject independent variable diagnostic group (DEP, ANX, HC) and the within subject independent variable film clip using the four ΔRSA changed scores as dependent variables (i.e. happy, neutral, fearful, sad film clip).

To assess transdiagnostic associations of ΔRSA with depression, anxiety and stress symptomatology, an ANCOVA was run using the same within subject independent variable film clip (i.e. the four ΔRSA changed scores for the happy, neutral, sad, fearful movies). The between subject independent variable diagnostic group was replaced by the continuous covariates anxiety (score of the DASS-21 anxiety subscale), depression (score of the DASS-21 depression subscale, stress (score of the DASS-21 stress subscale).

Additional analyses and general analyses remarks

To assess the possible influence of gender and age respiration and psychotropic medication on RSA outcome measures, additional analyses including these putative confounds can be found in section 3 of the Supplementary Online Materials. As a result, confounds did not significantly impact the effects reported in this work.

To assess whether the effects we found for RSA measure are specific for the activity of the parasympathetic branch of the autonomous nervous system, an identical set of analyses as for RSA indices was also ran for...
skin conductance level data. Therefore, we compared skin conductance level during the baseline period as well as change in skin conductance level from baseline to viewing the four film clips between diagnostic groups. Also, an additional set of correlational analyses were run to assess the association of markers of sympathetic activity with the outcome of disorder specific CBT.

In general, for all analyses of variance, significant interactions and main effects were followed up with standard post-hoc means comparisons. 90%CI calculation for $\eta^2$ effect sizes were done with the MBESS R-package. All other statistical tests were performed with IBM-SPSS (Version-28) with an alpha level of 0.05.

**Prediction of treatment outcome**

Prediction of treatment outcome with RSA was done in two steps. In a first step, we assessed the simple associations between RSA indices (i.e. $r_{RSA}$ and $\Delta RSA$ towards each of the four film clips) and treatment outcome as assessed (i.e., residual general distress changed score and the global success rating) using Pearson Correlations. To test for group differences (i.e. depression vs. anxiety) in these associations, Fisher Z Tests were calculated.

In a second step, we conducted additional structural equation modeling on the $\Delta RSA$ data. With this analysis we aimed at testing 1) whether $\Delta RSA$ towards the different emotional film clips represents the outcome of a common underlying emotion adaptation process (i.e. $\Delta RSA$ towards the four film clips should co-vary) or if $\Delta RSA$ towards the four clips represent unique processes (i.e. $\Delta RSA$ towards the four film clips should not co-vary) and 2) if a latent underlying variable $\Delta RSA_{latent}$ could be used to predict treatment outcome. Therefore, we first modelled a single latent variable using $\Delta RSA$ towards the four film clips as predictors. Next, we predicted treatment outcome with the new latent variable $\Delta RSA_{latent}$ using residual general distress and the global success rating as dependent variables. The fit of the measurement model (i.e. $\Delta RSA_{latent}$) was estimated and its fit prior to estimating structural models was ensured. CFI and TLI values greater than .95 and RMSEA values below .08 generally constitute good fit. Then, structural equation models were estimated, one for the whole group of patients, and one each for the two patient groups separately (DEP and ANX). All the models were conducted with IBM AMOS (Version 28).

**Results**

**RSA**

Of the initial participants who participated in the film viewing task, data of 2 healthy control participant, 14 depressed patients and 11 anxiety patients were lost due to equipment malfunction. The final sample for RSA analysis thus comprised of $n=58$ healthy controls, $n=91$ depressed patients, and $n=80$ anxiety patients.

Are there diagnose-based differences in $r_{RSA}$?

When patient groups were defined with respect to the patients primary diagnose (i.e. without taking co-morbidity into account) the ANOVA revealed a main effect for diagnostic group, $F(2, 228)=13.04, p<.001$, $\eta^2 = .103, 90\%CI [0.037, 0.178]$. Post hoc means comparisons showed that $r_{RSA}$ was higher in healthy controls as compared to patients with depression, $M_{Diff} = 1.26, 95\%CI [0.78, 1.75], p<.001$, and patients with anxiety disorders, $M_{Diff} = 0.70, 95\%CI [0.20, 1.20], p =.006$. Moreover, patients with anxiety disorders showed significantly higher $r_{RSA}$ than patients with depressive disorders, $M_{Diff} = 0.56, 95\%CI [0.12, 1.01], p =.013$.

Are there transdiagnostic associations with $r_{RSA}$

Simple correlations indicate that, higher depression, $r=-.246, p<.001$ and anxiety symptom load, $r=-.207, p=.002$, but not stress symptomatology, $r=-.068, p=.309$ were associated with less $r_{RSA}$. The regression analysis simultaneously including depression and anxiety symptoms as predictors revealed a significant regression equation, $F(1,224) = 7.87, p<.001, R^2 = 0.066$. Less $r_{RSA}$ was significantly associated with higher symptom load on the depression, $\beta = -.191, p=.019$, but not on the anxiety subscale, $\beta = -.093, n.s.$
Do the film clips elicit significant RSA reactivity as compared to the resting baseline (ΔRSA)?

Figure 1 (A) left panel gives an overview about RSA levels at rest and while viewing the four film clips. As expected the ANOVA revealed a significant main effect for episode, F (4,876)=16.33, p<.001, $\eta^2 = .069$, 90%CI [0.042, 0.094]. Standard means comparisons revealed that RSA was significantly higher during the resting baseline as compared to all of the four film clips (Resting Baseline vs. Happy: $M_{\text{Diff}} = 0.38, 95\%\text{CI [0.26, 0.49]}, p < .001$; Resting Baseline vs. Neutral: $M_{\text{Diff}} = 0.31, 95\%\text{CI [0.21, 0.42]}, p < .001$; Resting Baseline vs. Fear: $M_{\text{Diff}} = 0.23, 95\%\text{CI [0.12, 0.34]}, p < .001$; Resting Baseline vs. Sad: $M_{\text{Diff}} = 0.20, 95\%\text{CI [0.09, 0.31]}, p < .001$).

Are there diagnose-based differences in ΔRSA?

ΔRSA differed significantly between the four film clips (see figure 1B) as qualified by a significant main effect for film clip, F (3, 651) = 5.78, p < .001; $\eta^2 = .026$, 90%CI [0.005, 0.046]. Post hoc means comparisons showed that ΔRSA was largest for the happy film clip, differing significantly from the threatening, $M_{\text{Diff}} = -0.14, 95\%\text{CI [-0.22, -0.06]}, p < .001$ and sad film clip, $M_{\text{Diff}} = -0.17, 95\%\text{CI [-0.26, -0.08]}, p < .001$. Furthermore, ΔRSA differed significantly between the neutral and the sad film clip, $M_{\text{Diff}} = -0.11, 95\%\text{CI [-0.20, -0.01]}, p = .025$. There were no more significant differences in ΔRSA between the film clips.

There were no differences in ΔRSA between the diagnostic groups as indicated by a non-significant between subject independent variable diagnostic group, F (1, 217) = 1.29, p = .276, and a non-significant interaction film clip x diagnostic group, F (6, 651) = 0.55, p = .770.

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The ANCOVA revealed that overall, less ΔRSA was significantly associated with higher depression symptomatology, F(1, 214) = 8.32, p = .004; $\eta^2 = .037$, 90%CI [0.007, 0.087] but not significantly associated with anxiety, F(1, 214) = 0.02, n.s., or stress symptomatology, F(1, 214) = 3.58, n.s. There were no significant interactions between the within subject independent variable film clip and the depression, anxiety or stress scales of the DASS.

Prediction of treatment Outcome with markers of RSA

Data from n =77 patients with depressive and n =60 patients with anxiety disorders were available for analyses. The remaining patients either did not attend the post-treatment questionnaire assessment (n=23) or prematurely terminated their treatments (n=27). Data of 9 patients were lost due to technical reasons. Importantly, patients who dropped out did not differ from those who continued the study in their gender, age, nor their depression, anxiety, or stress symptoms scores (all p>.10).

Table 2 gives an overview about significant simple associations between treatment outcome and rRSA as well as ΔRSA towards the different film clips. In sum, rRSA was not significantly associated with the two treatment outcome measures, neither for depressed, nor for patients with anxiety disorders. In the contrary, enhanced ΔRSA towards all of the four film clips (i.e. more RSA withdrawal) was associated with better treatment outcome on both outcome measures - i.e. residual symptom score (see Figure 1 C lower panel) and the global success rating (see Figure 1 C upper panel) - in the group of depressed patients, but not in the group of anxiety patients. Moreover, Fisher-Z tests confirm that with the exception of ΔRSA towards the happy film clip, all correlation coefficients were significantly larger in the depression, as compared to the anxiety group (see Table 2).

To test whether ΔRSA towards the four film clips represent independent processes or are all the outcome of a single underlying process, we performed structural equation modelling. We first modelled a single latent variable using ΔRSA towards the four film clips as predictors. As a results, we found that the resulting measurement model for the ΔRSA$_{\text{latent}}$ variable fits the data very well, $\chi^2 (2) = 0.779, p = .677$, $CFI=1.000$, $RMSEA = .000$, 90%CI [0.000–0.107]. In a second step the latent model (see Figure 2) was conducted separately for the entire group of patients and for the depression and anxiety groups alone using ΔRSA$_{\text{latent}}$ as predictor and the two treatment outcome measures as dependent variables. For the entire group of patients
(i.e. depression and anxiety), more pronounced RSA withdrawal towards the film clips in terms of smaller ΔRSA values predicted better treatment outcome in terms of larger global success ratings ($\beta = -.217, p = .020$) and less post treatment residual general distress ($\beta = .196, p = .037$).

This pattern was evident also for the depressed patients alone (global success ratings, $\beta = -.358, p = .002$, post treatment residual general distress, $\beta = .312, p = .009$). However, for anxiety patients alone, latent ΔRSA neither significantly predicted the global success rating ($\beta = .003, p = .958$) nor the residual symptom score ($\beta = -.057, p = .692$).

**Skin Conductance Level**

**Individual differences in Skin Conductance Level during Baseline**

We did not find any differences between the diagnostic groups in Skin Conductance Level during the resting baseline condition, $F(2, 222) = 1.40, p=.250$.

**Skin Conductance Level during film clip viewing**

As evidenced by a significant main effect for episode, $F(4,872) = 44.05, p<.001, \eta^2 = .168, 90\%CI [0.129, 0.202]$, participants exhibited significantly higher skin conductance level while viewing the film clips as compared to the baseline condition. Single post hoc means comparisons indicate that this was true for the happy, $M_{Diff} = -0.64, 95\%CI [-0.76, -0.52], p <.001$, neutral, $M_{Diff} = -0.59, 95\%CI [-0.71, -0.48], p <.001$, threatening, $M_{Diff} = -0.61, 95\%CI [-0.73, -0.49], p <.001$, and sad film clip, $M_{Diff} = -0.61, 95\%CI [-0.77, -0.45], p <.001$. There was no significant main effect for diagnostic group, $F(2,218) = 0.99, p=.372$; nor a significant interaction for diagnostic group x episode, $F(8,872) = 0.59, p=.688$.

**Prediction of treatment outcome with Skin Conductance Level**

We did not find any significant associations between skin conductance level during baseline or skin conductance change from baseline to viewing the film clips and any treatment outcome measure (all $p >.10$).

**Discussion**

Here, we assessed (1) the significance of resting Respiratory Sinus Arrhythmia (rRSA) and Respiratory Sinus Arrhythmia reactivity (ΔRSA), two markers of cardiac vagal control for the mood and anxiety disorders spectrum as well as (2) the predictive validity these markers have for the outcome of disorder specific CBT. In line with our hypotheses, the group-based approach demonstrated that patients regardless of diagnose exhibited significantly lower rRSA than healthy controls. However, transdiagnostically, we found a more robust association of RSA indices with depression symptomatology. In specific, depression, but not anxiety symptomatology was transdiagnostically associated with more favorable rRSA and ΔRSA. Furthermore, confirming a more robust association between depression symptomatology and RSA, the current study shows for the first time that more favorable ΔRSA is predictive of more favorable treatment outcome in depression, but not in anxiety. Importantly, we did not find any effect for skin conductance level, a physiological marker specifically reflecting the activity of the sympathetic branch of the autonomous nervous system (ANS). This indicates specificity of the current findings for the activity of the parasympathetic branch of the ANS. In addition, these current results were not affected by interindividual differences in respiration, psychotropic medication, age or gender.

As expected, the group-based analysis showed that patients with mood and anxiety disorders displayed significantly lower rRSA than healthy controls. This finding is in line with meta-analyses showing that internalizing disorders are associated with reduced rRSA. As stated in the neurovisceral integration model high levels of rRSA reflect the activity of a top-down regulation system involved in the organisms flexible physiological responding to emotional or stress related environmental demands. rRSA has been previously associated with behavioral flexibility, cognitive executive functioning and self-regulation, processes frequently impaired in mood and anxiety disorders. Moreover, following the neurovisceral integration model RSA is associated with activation of the medial Prefrontal Cortex a heterogeneous neural structure critically involved.
in a wide range of emotional processes. Out data are thus in line with previous research attributing impairments in prefrontal cortex functioning to both disorders.

Despite the overall significance of RSA for disorders from the mood and anxiety disorders spectrum, its differential relationship with depression and anxiety symptomatology seems to be more complex. Indeed, although the group-based analyses indicate that both patients with anxiety and depression exhibit reduced rRSA, the transdiagnostic analysis (across the entire mood and anxiety disorders spectrum and healthy controls) simultaneously including questionnaire-based depression and anxiety symptomatology as predictors showed that higher symptoms of depression, but not anxiety, predicted lower rRSA. That is, depression-symptomatology explained most of the variance anxiety-symptomatology shared with rRSA. This clearly suggest a more robust transdiagnostic association between depressive symptomatology and rRSA in a direct comparison with anxiety symptoms. This specific association of rRSA with depression symptomatology is paralleled by the ΔRSA results. That is, that also less ΔRSA was transdiagnostically (i.e. across the entire sample) associated with higher depression— but not anxiety symptomatology. This association was not restricted to the sadness-inducing film clip, but rather broadly distributed over the full range of emotional clips. This indicates that broad blunted ΔRSA is specifically associated with more severe depression symptomatology. These data thus are in line and extend current meta-analyses associating depression but not anxiety with less favorable ΔRSA. Paralleling this, while depression and anxiety share a liability to experience negative affect, both disorders are distinguishable on basis of their emotional reactivity. That is, an impressive number of studies show that most (but not all) anxiety-disorders are related to processing deficits towards specific, individually fear relevant stimuli. In the contrary, indicating sustained context insensitivity in depression, depression is related to broad blunted affective reactivity towards a diverse range of emotional challenges, including reactivity towards neutral stimulus materials. This striking link between broad blunted ΔRSA in the current study and blunted affective reactivity as shown in the literature, is further supported by findings indicating that ΔRSA predicts subjective responses towards film-based mood inductions. Moreover, in general, RSA is dependent on the momentary amount of cognitive involvement, whereby more cognitive involvement is associated with higher vagal reactivity. Taken together, the current data further support and extend on previous findings on emotion context insensitivity in depression. They clearly highlight a specific association of ECI with depression symptomatology rather than anxiety symptoms and at the same time shows the transdiagnostic relevance emotion context insensitivity has across naturalistic comorbid sample of patients from the internalizing symptoms spectrum. Thus, the current data might suggest the usefulness of ΔRSA as a transdiagnostic biomarker for depression-symptom-based ECI across the mood and anxiety disorders spectrum.

Further substantiating the specific associations we found between depression-symptomatology and RSA, our data show specific predictive validity of ΔRSA for treatment outcome in patients with depression. In fact, more favorable ΔRSA (more RSA withdrawal) specifically predict better treatment outcome in depression (i.e. on both outcome measures). No such association was found for anxiety disorders. Only very few studies so far investigated the predictive validity of ΔRSA. Rottenberg and colleagues showed that more pronounced vagal withdrawal to a sad film predicts recovery from depression and less symptom severity at 6 month follow-up while others did not find any association between ΔRSA and the outcome of a CBT intervention in anxiety disorders. Our data complement this work and shows for the first time specific predictive validity of ΔRSA for the outcome of multi session CBT treatments in depressive disorders. It has to be determined if the current findings reflect the physiological readout of a specific mechanism in the depression treatments. The fact that there was no association between ΔRSA and symptom reduction from pre to post treatment in the anxious group, might suggest that the predictive relationship between ΔRSA and treatment outcome in depression is not solely based on spontaneous symptom recovery. Moreover, as compared to anxiety, emotional or regulative processes are among the core mechanisms of change within treatments of depressive disorders, while anxiety-treatment frequently target exposure techniques, with extinction learning as a key mechanism of change. In line with this, it has been shown that CBT enhances global cognitive control network activity in depression as well as emotion regulation abilities, processes which have been previously associated with RSA. Moreover, our data support previous findings that broad
improvement of affect-regulation capacity, including adaptation processes towards emotion stimulation and their neuronal underpinnings might be specific mechanisms of change within depression-specific CBT. Especially in line with this, predictive validity of ΔRSA was again not restricted to vagal withdrawal towards the “disorder-specific” sadness inducing stimulus only. In the contrary, our data indicate that more favorable vagal withdrawal towards all movies predicted better treatment outcome. Again, these data are clearly in line with the predictions of the emotion context insensitivity theory and indicate that less context insensitivity in vagally mediated emotional responses predict better CBT outcome. Thus, supporting previous reports of improvements in vagally mediated heart rate variability after a CBT intervention in depression the current data further point to ΔRSA as a specific marker for treatment change in depression. However, clearly further research is needed to substantiate this specific predictive validity of ΔRSA as a physiological indicator of emotion adaptation processes as a depression-specific mechanism in mood disorders.

The remarkable dissociations between our group-based and our transdiagnostic analyses in both rRSA and ΔRSA speaks in favor of recent attempts to develop psychometrically robust dimensional classification systems like the hierarchical taxonomies of mental disorders (HiTop, Kotov et al., 2017) or the Research Domain Criteria Framework (RDoC, Cuthbert, et al., 2014). A transdiagnostic approach might be more sensitive to detect subtle interindividual differences in heterogeneous samples like the current one yielding high comorbidity rates. However, overall the effect sizes were comparably small and thus our data should be interpreted with some caution. They nonetheless can serve as starting points for future research into the common and distinct associations between RSA and depression and anxiety. Our data further support current theoretical models highlighting the usefulness of RSA as a transdiagnostic biomarker cutting across traditional diagnostic categories. They thus complement previous research showing a transdiagnostic association of RSA with suicide ideation. Furthermore, in showing a common association between RSA across depression and anxiety disorders, our data is in line with the idea of a general factor underlying the mood and anxiety disorders spectrum, and are broadly compatible with the ideas of the Research Domain Criteria initiative to identify transdiagnostic biomarkers for specific cognitive or emotional processes which operationalize mental disorders to fall along a continuum ranging from normal to disordered functioning.

Caveats

Our study comes with limitations. First, we recruited a naturalistic, ecologically valid sample of patients receiving treatment-as-usual in our outpatient center. Thus, closely monitoring the therapeutic process, as usually conducted in randomized controlled trials, was not possible. Enhanced ecological validity of the current samples and the treatment process most likely caused limitations in treatment integrity. However, as mentioned above, treatments in our center regularly follow published Cognitive Behavior Therapy manuals and treatment sessions are monitored regularly by trained supervisors (von Brachel et al., 2019) assuring general adherence to treatment manuals. Moreover, although disorder-specific manuals are used, all manuals cover Cognitive Behavior Therapy and all anxiety manuals are comparable in being exposure-based. Second, a considerable amount of patients did not attend the post-treatment questionnaire assessment or terminated the treatment prematurely (see results section for details). This resulted in a considerable reduction in power of our analyses concerning prediction of treatment outcome. However, the current response-rate is comparable to previous studies in outpatient settings (von Brachel et al., 2019), and patients who finished the study, and those who dropped out did not differ from each other in terms of, rRSA, ΔRSA, gender, age, or their depression, anxiety or stress level. Moreover, because we recruited a large patient sample, the final N for the prediction of treatment outcome was still considerably high (n =135), nonetheless yielding considerable statistical power. Thus, it is unlikely that the current effects were severely affected by the current drop-outs.

Third, since the current study had been started before the final release of the DSM-5 in Germany, the now outdated DSM-IV classification system has been used in the present study. As a result, the current anxiety sample includes patients with obsessive compulsive disorder as well as with posttraumatic stress disorder, which within the DSM-5 are no longer considered anxiety disorders. However, we carried out a set of analyses excluding patients with an OCD and a PTSD diagnosis. In fact, the results yielded results similar to the
original analyses carried out including the OCD and PTSD patients. Thus, the inclusion of these patients did not significantly bias the current findings.

Clearly, future studies are needed to clarify if the more pronounced association between RSA and depression is a function of the depression symptomatology per se, or of higher symptom load in the depressed sample. Indeed, more severe burden of disease has been attributed to depression as compared to a multitude of somatic widespread diseases or other mental disorders including anxiety. As depression and anxiety are often accompanied by significant dysregulation of the stress system they have an enhanced risk of developing cardiovascular diseases. Stress and CVD are themselves associated with lowered heart rate variability, complicating the interpretation of the current findings. The high comorbidity between depression and anxiety disorders, in addition to the fact that some anxiety disorders are more likely to precede the onset of depression while others onset secondary to depression, underscores the need for further studies to disentangle the putatively intertwined mechanisms underlying the association between psychopathological states and RSA. Finally, we did not assess income, education and socioeconomic status. This putatively hamper generalizability of the current data.

Conclusion

Taken together, the current data support theoretical considerations on the significance of indices of RSA as transdiagnostic biomarkers relevant for the mood and anxiety disorders spectrum. At the same time, our data provide convincing first evidence that this transdiagnostic association is more pronounced for depression-rather than anxiety-symptomatology. This highlights the importance of recognizing symptom comorbidity within experimental approaches towards mechanisms underlying the mood and anxiety disorders spectrum. Moreover, the current data show, that mechanistic transdiagnostic approaches are more sensitive for detecting interindividual difference in naturalistic clinical sample. Thus, the current findings clearly support current attempts to develop psychometrically robust, transdiagnostic and dimensional clinical measures, like the hierarchical taxonomies of mental disorders (HiTop, Kotov et al., 2017) or the Research Domain Criteria Framework (RDoC, Cuthbert et al., 2014) allowing for an ecologically valid assessment of psychopathology and overcome known issues with current nosologies (Michelini et al., 2021). Furthermore, our data suggest a more robust transdiagnostic association of (at least) ΔRSA with depression and thus suggest that rRSA and ΔRSA constitute potential transdiagnostic biomarkers enabling to assess common and distinct emotion-related mechanisms associated with the depression and anxiety spectrum.

Footnotes

1 The current sample of patient is representative for the entire patient population attending for treatment at our outpatient center during the period of data assessment for the current study in terms of distribution of diagnoses, $\chi^2 (2) = 2.67, p = .263$, gender, $\chi^2 (2) = 0.23, p = .629$, and age, $t (1827) = 0.80, p = .425$.

2 An interstimulus interval of 1 minute has been shown to be sufficient for the recovery of vagal activity after exposure to a psychological stressor (e.g. Mezzacappa et al., 2001)

Supplementary Material

The Supplementary Materials File submitted along with the main manuscript covers detailed information about the CBT manuals used for the patients’ treatments, a comprehensive description of the validation of the film clips used in the emotion induction paradigm, and a comprehensive set of analyses controlling for putatively influencing factors (i.e. gender, age, respiration and medication) on our RSA analyses.

Table 1. Descriptive statistics of demographic variables and symptomatology for the three diagnostic groups

<table>
<thead>
<tr>
<th></th>
<th>DEP</th>
<th>ANX</th>
<th>HC</th>
<th>Group Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age M (SD)</td>
<td>39.54 (14.68)</td>
<td>34.14 (11.91)</td>
<td>33.19 (11.29)</td>
<td>$F(2,249) = 6.04, p = .003^{1,3}$</td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>42/61</td>
<td>39/54</td>
<td>14/64</td>
<td>$\chi^2 (2) = 6.40, p = .041^{1,2}$</td>
</tr>
<tr>
<td>Psychotropic medication (yes/no)</td>
<td>56/47</td>
<td>33/60</td>
<td>0/60</td>
<td>$\chi^2 (2) = 49.45, p &lt; .001^{1,2,3}$</td>
</tr>
</tbody>
</table>
Table 2. Correlations of RSA indices with the post treatment global success rating (upper part) and Residual Symptom Change Score (lower part) for Depressed Patients and Anxiety Patients

<table>
<thead>
<tr>
<th></th>
<th>Depression</th>
<th>Anxiety</th>
<th>Group Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>rRSA</td>
<td>0.093 n.s.</td>
<td>0.193 n.s.</td>
<td>r = -0.54 n.s.</td>
</tr>
<tr>
<td>(\Delta R\Sigma A_{\text{hap}})</td>
<td>-0.322 (p&lt;.01)</td>
<td>-0.226 n.s.</td>
<td>z = -0.54 n.s.</td>
</tr>
<tr>
<td>(\Delta R\Sigma A_{\text{neut}})</td>
<td>-0.258 (p&lt;.05)</td>
<td>0.107 n.s.</td>
<td>z = -1.95 (p&lt;.05)</td>
</tr>
<tr>
<td>(\Delta R\Sigma A_{\text{threat}})</td>
<td>-0.310 (p&lt;.05)</td>
<td>0.036 n.s.</td>
<td>z = -1.88 (p&lt;.05)</td>
</tr>
<tr>
<td>(\Delta R\Sigma A_{\text{sad}})</td>
<td>-0.269 (p&lt;.05)</td>
<td>0.083 n.s.</td>
<td>z = -1.89 (p&lt;.05)</td>
</tr>
</tbody>
</table>

DASS General Distress Residual Gain Score

<table>
<thead>
<tr>
<th></th>
<th>Depression</th>
<th>Anxiety</th>
<th>Group Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>rRSA</td>
<td>-0.056 n.s.</td>
<td>-0.135 n.s.</td>
<td>z = 0.42 n.s.</td>
</tr>
<tr>
<td>(\Delta R\Sigma A_{\text{hap}})</td>
<td>0.268 (p&lt;.05)</td>
<td>0.095 n.s.</td>
<td>z = 0.94 n.s.</td>
</tr>
<tr>
<td>(\Delta R\Sigma A_{\text{neut}})</td>
<td>0.250 (p&lt;.05)</td>
<td>-0.086 n.s.</td>
<td>z = 1.80 (p&lt;.05)</td>
</tr>
<tr>
<td>(\Delta R\Sigma A_{\text{threat}})</td>
<td>-0.269 (p&lt;.05)</td>
<td>-0.062 n.s.</td>
<td>z = 1.78 (p&lt;.05)</td>
</tr>
<tr>
<td>(\Delta R\Sigma A_{\text{sad}})</td>
<td>0.236 (p&lt;.05)</td>
<td>-0.080 n.s.</td>
<td>z = 1.69 (p&lt;.05)</td>
</tr>
</tbody>
</table>

Note: hap=happy film clip, neut=neutral film clip, threat=threatening film clip, sad=sad film clip, n.s.=non-significant

Figure Headings

Figure 1. (A) RSA level during baseline and while viewing the four film clips. (B) RSA change from baseline (i.e. \(\Delta R\Sigma A\), film clip – baseline) for the four film clips. (C) Scatterplots for the correlations between \(\Delta R\Sigma A\) and treatment outcome for the Global Success Rating (upper panel) and the residual symptom change score (lower panel). Bold lines represent regression lines for the group of depressed patients, dotted lines for the anxiety patients.

Figure 2. Structural equation model for the prediction of treatment outcome with the Residual Symptoms Score and the Global Success Rating. Note: ***\(p<.001\), **\(p<.01\), *\(<p.05\); Standardized regression coefficients for the entire group of patients are given on the arrows as follows: All Patients/ Depressed Patients/ Anxiety Patients.
Figure 1

Figure 2.