

Pre-treatment cardiac vagal tone predicts dropout from and residual symptoms after exposure therapy in patients with panic disorder and agoraphobia

- Supplementary methods and results -

Methods and Materials

Participants

Three hundred and one patients with a principle diagnosis of panic disorder with agoraphobia (PD/AG), enrolled for the multicenter randomized clinical trial study Mechanisms of Action in Cognitive Behavioral Therapy [1–3], underwent exposure-focused psychotherapy (please see [1,2] for patient recruitment, inclusion/ exclusion criteria, randomization procedures, and information on wait-list controls). Diagnosis of PD/AG was established by a standardized interview [4,5]. All patients were consistent with the demographics of the population and free from psychotropic medication. Patients gave written informed consent after receiving a detailed description of the study. The study was approved by the Ethics Committee of the Medical Faculty of the Technische Universität Dresden.

Treatment

After inclusion in the clinical trial, patients received a 12-session manualized treatment protocol, implemented over six weeks. The protocol included psychoeducation, functional analysis, interoceptive exposure, and exposure in situ in standard as well as ideographically salient situations (see [1,2] for a detailed description). Therapists were trained during a 3-day training workshop and were certified by the coordination center. Treatment dropout including its reason (e.g. “not motivated for exposure”, “too afraid to enter exposure situation”, “moved to another city”, “no agreement between treatment and work schedule”) was documented between baseline and post assessment.

Outcome Assessment

The Clinical Global Impression Scale (CGI; [6]) is a clinician-rated scale that measures the overall severity of a disorder, with scores that range between 1 (no disorder) and 7 (among the most severely ill patients). In order to maximize reliability, we instructed interviewers to consider panic symptoms, anxiety, anticipatory anxiety, avoidance, and functional level before making the global rating. The rating, thus, represents a global assessment of the patient's PD/AG symptom severity and functioning.

Other primary outcome variables of the clinical trial included the Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A; [7]), the number of panic attacks as reported in the Panic Agoraphobia Scale (PAS; [8]), and intensity of agoraphobic avoidance as measured by the Mobility Inventory (MI; [9]). All variables were assessed prior to treatment onset (baseline), prior to exposure in vivo sessions (intermediate assessment), after treatment completion (post assessment), and at a 6-month follow up [1]. For the purpose of the present analysis, we focused on results from baseline and post assessments.

Assessment of Pre-Treatment Heart Rate Variability (HRV)

HRV assessment was based on electrocardiogram (ECG) data collected during a highly standardized behavioral avoidance test (BAT; [10]) which followed baseline assessment and was conducted prior to therapy onset in all participating centers. In short, the BAT consisted of a standardized exposure to a small, dark, and closed test chamber for a maximum duration of 10 minutes following a 10-minute anticipation phase in which patients were instructed to sit in front of the opened test chamber. After exposure and following a five minutes break, patients were instructed to sit quietly again in front of the opened chamber for an 8-minute resting period. ECG was measured continuously during the whole BAT assessment. The first five minutes of the relaxation period, during which no further stimuli were presented, were used to determine HRV. Intensity of experienced anxiety and panic were assessed immediately after

each phase on a 10-point Likert scale ranging from 1 (not at all) to 10 (very strong). Mean reported anxiety during the resting phase was very low ($m=2.18$, $SD=1.51$).

ECG recording was controlled by personal computers running the software VPM [11] and executed with an Eindhoven Lead II setup with two standard Ag/AgCl electrodes (8 mm; Marquette Hellige, Freiburg, Germany). The ECG signal was filtered online with an 8 to 13 Hz bandpass filter, amplified with the factor 2000, and sampled at a rate of 1000 Hz using a Coulbourn V75-04 bioamplifier (Allentown, PA). Then, the ECG signal was down-sampled to 400 Hz, visually inspected and artifact-corrected using ANSLAB [12]. HRV Analysis [13] was used to determine time- and frequency-domain measures of vagally mediated HRV, that is, the root mean square of successive RR intervals (RMSSD) and high frequency (HF; frequency band: 0.15-0.40 Hz) HRV. Absolute power (ms^2) of HF-HRV was determined using fast Fourier transform (FFT) as implemented in HRV Analysis. Prior to all analyses, RMSSD and HF-HRV were logarithmized (natural log) to account for deviations from normal distribution and unequal sample sizes.

Data Analysis

Of those 301 patients who underwent exposure-focused psychotherapy, ECG data for HRV analyses was available from 249 patients¹. Of those, 20 patients took beta-blockers, which are known to alter HRV [14], and were therefore excluded from further analyses. Finally, one patient was excluded due to a missing CGI score at post assessment resulting in a final sample of 228 patients (174 women) with a mean age of 34.38 years ($SD = 10.36$).

All statistical tests were performed using IBM SPSS Statistics 24.0 (SPSS Inc., Chicago, IL, USA). In a first step, potential predictors for residual symptoms and treatment dropout were checked for associations between themselves as well as for between-groups differences.

¹ Five patients did not participate in the BAT, 16 patients discontinued the BAT assessment prior to the final resting period, and ECG data from 31 patients was lost due to equipment failure.

Spearman correlation analyses were used to investigate associations of HRV indicators (RMSSD, HF-HRV) with age and body mass index (BMI) [15] as well as baseline symptom severity. Independent t-tests were conducted to test for significant differences between men and women as well as between smokers and non-smokers. Independent t-tests were also conducted to test for significant differences regarding baseline levels of symptom severity as well as pre-treatment levels of HRV between the fully recovered group and the group with residual symptoms as well as the treatment dropout group. As an additional exploratory analysis, we also compared pre-treatment RMSSD and HF-HRV in those patients who dropped out due to motivational reasons (N = 16; e.g., “not motivated for exposure exercise”, “too much fear to enter exposure situation”) and those who claimed other reasons (N = 23; e.g., “moved to another city”, “no agreement between treatment and work schedule”) again using independent t-tests.

In a second step, we conducted binary logistic analyses with the categorical dependent variable “residual symptoms vs full recovery” and either RMSSD (RMSSD model) or HF-HRV (HF-HRV model) as predictor variables to test whether HRV predicts residual symptoms as opposed to full recovery. To test the individual contribution of HRV indices when predicting residual symptoms, HRV indices were introduced in a single step together with those demographic and baseline symptom severity variables that showed the highest discrimination between groups. The same procedure was applied to test whether HRV predicts treatment dropout as opposed to full recovery. All regression analyses used the model coefficient (Omnibus test), Nagelkerke’s R^2 , classification performance, and Wald statistic as statistical criteria.

Results

Sample Characteristics

Pre-treatment levels of HRV did not differ between men and women (RMSSD: $t(226) = 0.20$, $p = .840$; HF-HRV: $t(226) = 1.01$, $p = .315$) or between smokers and non-smokers (RMSSD:

$t(226) = 0.43, p = .670$; HF-HRV: $t(226) = 0.06, p = .950$). Confirming previous findings [15], HRV decreased with older age (RMSSD: $r(228) = -.251, p = .000$; HF-HRV: $r(228) = -.268, p = .000$) and higher BMI (RMSSD: $r(210) = -.202, p = .000$; HF-HRV: $r(210) = -.208, p = .000$). As evident from Table S1, however, neither the group with residual symptoms nor the treatment dropout group differed significantly from the fully recovered group with regard to these variables.

Table S1. Distribution of gender, smoking status, age, BMI, and symptom severity during baseline assessment in three study groups.

	Recovered (N = 28)	Residual symptoms (N = 161)	Treatment dropouts (N = 39)	Statistics	
	N (%)			Recovered vs Residual symptoms	Recovered vs Treatment dropouts
Women	25 (89.3)	119 (73.9)	30 (76.9)	$\chi^2(1) = 3.11, p = .08$	$\chi^2(1) = 1.69, p = .19$
Smokers	12 (42.9)	68 (42.2)	15 (38.5)	$\chi^2(1) = 0.00, p = .95$	$\chi^2(1) = 0.13, p = .72$
	Mean (SD)				
Age (Years)	32.25 (10.13)	34.50 (10.72)	35.41 (8.98)	$t(187) = 1.03, p = .30$	$t(65) = 1.35, p = .18$
BMI (kg/m ²)	23.61 (3.74)	23.90 (4.60)	24.35 (4.38)	$t(174) = 0.30, p = .77$	$t(58) = 0.69, p = .49$
CGI (1-7)	4.96 (0.74)	5.19 (0.74)	5.15 (0.78)	$t(187) = 1.46, p = .15$	$t(65) = 1.00, p = .32$
SIGH-A (0-56)	22.32 (5.88)	23.70 (6.92)	23.43 (7.73)	$t(187) = 0.99, p = .32$	$t(65) = 0.64, p = .53$
Number of PA	2.36 (2.41)	2.61 (2.34)	2.44 (2.64)	$t(187) = 0.52, p = .60$	$t(65) = 0.13, p = .90$
MI Alone (1-5)	2.85 (0.73)	3.01 (0.75)	2.87 (0.79)	$t(168) = 0.96, p = .34$	$t(57) = 0.11, p = .91$

Due to missing values, BMI scores and MI Alone scores were available only in 210 patients (Recovered: N = 26; Residual symptoms: N = 150; Treatment dropouts: N = 34) and 203 patients (Recovered: N = 26; Residual symptoms: N = 144; Treatment dropouts: N = 33), respectively. A patient was classified as a smoker if on average at least one unit of tobacco on each day during the last 4 weeks was reported. BMI, Body Mass Index; CGI, Clinical Global Impression Scale; SIGH-A, Structured Interview Guide for the Hamilton Anxiety Scale; Number of PA = number of panic attacks during the last week reported in the Panic and Agoraphobia Scale; MI Alone, Mobility Inventory, alone subscale.

Pre-treatment HRV was not associated with baseline levels of symptom severity as indicated by overall disorder severity and functioning (CGI), severity of anxiety symptoms (SIGH-A),

number of panic attacks in the previous week, and agoraphobic avoidance behavior (MI Alone); all $r_s < .10$. Furthermore, as shown in Table S1, neither the group with residual symptoms nor the treatment dropout group differed from the fully recovered group with regard to baseline levels of symptom severity.

In addition to the results reported in the main text, exploratory analyses revealed that within the treatment dropout group, pre-treatment HRV levels were particularly low in those patients ($N = 16$) stating motivational reasons for discontinuing exposure treatment (RMSSD: $t(37) = 2.25, p = .030$; HF-HRV: $t(37) = 2.37, p = .023$; see Figure S1).

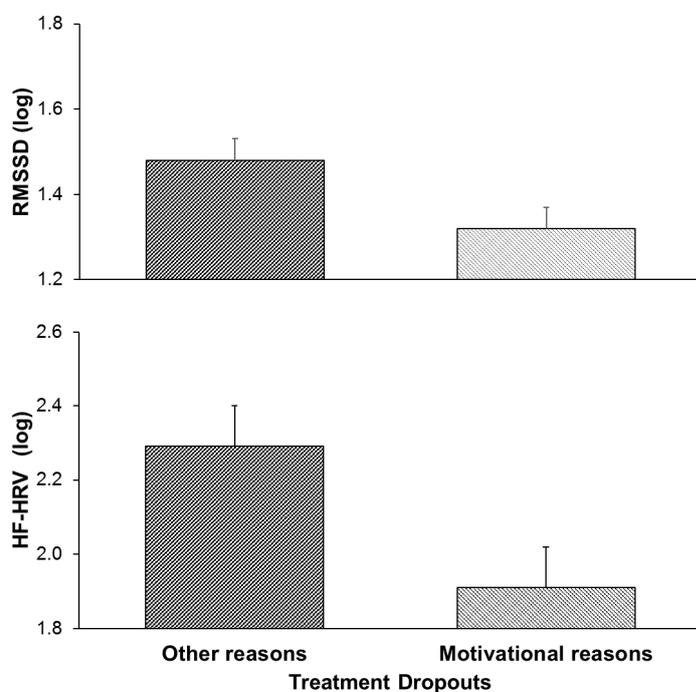


Figure S1. Pre-treatment levels of heart rate variability (HRV) in treatment dropouts who dropped out for motivational reasons (right) and those who dropped out for other reasons (left). Bar charts represent means and standard errors of logarithmized values from the root mean square of successive differences (RMSSD; upper panel) and high frequency (HF-)HRV (lower panel).

Prediction of Residual Symptoms by HRV

To predict residual symptoms, binary logistic regressions were conducted using either RMSSD or HF-HRV scores to indicate HRV together with sex and age as well as CGI scores as indicators of baseline symptom severity. Fully recovered patients served as a reference group. Tests of the full models against their respective constant only models were statistically significant (RMSSD: $\chi^2(4) = 11.23, p = .024$; HF-HRV: $\chi^2(4) = 11.19, p = .025$). Generally,

Nagelkerke's R^2 of .102 (RMSSD model) and .101 (HF-HRV model) indicated a low association between prediction and grouping. Relatively high ratios of correctly classified patients (84.7% with both the RMSSD model and the HF-HRV model) mostly reflect unequal group sizes for fully recovered patients and those with residual symptoms. As evident from Table S2, however, the Wald criterion indicated that only HRV made a significant contribution to predict residual symptoms (RMSSD: 4.27, $p = .039$; HF-HRV: 4.25, $p = .039$).

Table S2. Prediction of residual symptoms (binary logistic regressions).

RMSSD model						HF-HRV model					
Variable	Wald	p	Exp(B)	95% CI for Exp(B)		Variable	Wald	p	Exp(B)	95% CI for Exp(B)	
				Lower	Upper					Lower	Upper
Constant	0.78	.776	6.49			Constant	0.39	.535	3.30		
Sex	3.25	.071	3.28	0.90	11.95	Sex	2.97	.085	3.11	0.86	11.31
Age	0.30	.585	1.01	0.97	1.06	Age	0.25	.619	1.01	0.97	1.06
CGI	1.87	.171	1.48	0.85	2.58	CGI	1.93	.165	1.48	0.85	2.58
RMSSD	4.27	.039	0.17	0.03	0.91	HF-HRV	4.25	.039	0.42	0.18	0.96

CGI, Clinical Global Impression Scale; CI, Confidence Interval; RMSSD, root mean square of successive differences; HF-HRV, high frequency heart rate variability.

Prediction of Treatment Dropout by HRV

To predict treatment dropout, binary logistic regressions were conducted using either RMSSD or HF-HRV scores to indicate HRV together with sex and age as well as CGI scores as indicators of baseline symptom severity. Fully recovered patients served as a reference group. Tests of the full models against their respective constant only models were statistically significant (RMSSD: $\chi^2(4) = 10.83$, $p = .029$; HF-HRV: $\chi^2(4) = 9.18$, $p = .057$). Generally, Nagelkerke's R^2 of .201 (RMSSD model) and .172 (HF-HRV model) indicated a low association between prediction and grouping. Accordingly, only 64.2% of patients were correctly classified both with the RMSSD model and the HF-HRV model. As evident from

Table S3, however, the Wald criterion indicated that only HRV made a significant contribution to predict treatment dropout (RMSSD: 4.72, $p = .030$; HF-HRV: 3.40, $p = .065$).

Table S3. Prediction of treatment dropout (binary logistic regressions).

RMSSD model						HF-HRV model					
Variable	Wald	p	Exp(B)	95% CI for Exp(B)		Variable	Wald	p	Exp(B)	95% CI for Exp(B)	
				Lower	Upper					Lower	Upper
Constant	0.21	.643	3.96			Constant	0.06	.809	0.54		
Sex	2.06	.151	3.25	0.65	16.17	Sex	1.91	.167	2.99	0.63	14.17
Age	0.48	.488	1.02	0.96	1.09	Age	1.07	.302	1.03	0.97	1.09
CGI	1.47	.225	1.54	0.77	3.07	CGI	1.32	.250	1.49	0.75	2.95
RMSSD	4.72	.030	0.06	0.01	0.76	HF-HRV	3.40	.065	0.37	0.13	1.07

CGI, Clinical Global Impression Scale; CI, Confidence Interval; RMSSD, root mean square of successive differences; HF-HRV, high frequency heart rate variability.

References

- 1 Gloster AT, Wittchen HU, Einsle F, Höfler M, Lang T, Helbig-Lang S, et al.: Mechanism of action in CBT (MAC): methods of a multi-center randomized controlled trial in 369 patients with panic disorder and agoraphobia. *Eur Arch Psychiatry Clin Neurosci* 2009;259 Suppl:S155-66.
- 2 Gloster AT, Wittchen H-U, Einsle F, Lang T, Helbig-Lang S, Fydrich T, et al.: Psychological treatment for panic disorder with agoraphobia: a randomized controlled trial to examine the role of therapist-guided exposure in situ in CBT. *J Consult Clin Psychol* 2011;79:406–20.
- 3 Gloster AT, Hauke C, Höfler M, Einsle F, Fydrich T, Hamm A, et al.: Long-term stability of cognitive behavioral therapy effects for panic disorder with agoraphobia: A two-year follow-up study. *Behav Res Ther* 2013;51:830–839.
- 4 Essau CA, Wittchen HU: An overview of the Composite International Diagnostic Interview (CIDI). *Int J Methods Psychiatr Res* 1993;3:79–85.
- 5 Robins LN, Wing J, Wittchen HU, Helzer JE, Babor TF, Burke J, et al.: The Composite International Diagnostic Interview: An epidemiologic instrument suitable for use in conjunction with different diagnostic systems and different cultures. *Arch Gen Psychiatry* 1988;45:1067–1077.
- 6 Guy W: *ECDEU Assessment Manual for Psychopharmacology: Revised*. Rockville, MD, U.S. Department of Health, Education, and Welfare, 1976.
- 7 Shear MK, Vander Bilt J, Rucci P, Endicott J, Lydiard B, Otto MW, et al.: Reliability and validity of a Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A). *Depress Anxiety* 2001;13:166–178.
- 8 Bandelow B: *Panic and Agoraphobia Scale (PAS)*. Seattle, WA, Hogrefe & Huber Publishers, 1999.
- 9 Chambless DL, Caputo GC, Jasin SE, Gracely EJ, Williams C: *The Mobility Inventory*

- for Agoraphobia. *Behav Res Ther* 1985;23:35–44.
- 10 Richter J, Hamm AO, Pané-Farré CA, Gerlach AL, Gloster AT, Wittchen H-U, et al.: Dynamics of defensive reactivity in patients with panic disorder and agoraphobia: implications for the etiology of panic disorder. *Biol Psychiatry* 2012;72:512–20.
 - 11 Cook III EW, Atkinson L, Lang KG: Stimulus control and data acquisition for IBM PCs and compatibles. *Psychophysiology* 1987;24:726–727.
 - 12 Blechert J, Peyk P, Liedlgruber M, Wilhelm FH: ANSLAB: Integrated multichannel peripheral biosignal processing in psychophysiological science. *Behav Res Methods* 2016;48:1528–1545.
 - 13 Niskanen JP, Tarvainen MP, Ranta-Aho PO, Karjalainen PA: Software for advanced HRV analysis. *Comput Methods Programs Biomed* 2004;76:73–81.
 - 14 Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology: Heart rate variability. Standards of measurements, physiological interpretation, and clinical use. *Eur Heart J* 1996;17:354–381.
 - 15 Laborde S, Mosley E, Thayer JF: Heart rate variability and cardiac vagal tone in psychophysiological research - Recommendations for experiment planning, data analysis, and data reporting. *Front Psychol* 2017;8. DOI: 10.3389/fpsyg.2017.00213