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Heart rate variability in patients with agoraphobia with or without panic disorder remains stable during CBT but increases following in-vivo exposure

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ABSTRACT

Patients with anxiety disorders have a lower heart rate variability (HRV) than healthy controls. Low HRV is associated with cardiovascular disease and dysfunction of the autonomic nervous system (ANS). The aim of the present study was to investigate if HRV in patients with agoraphobia with or without panic disorder can be influenced by cognitive behavioral therapy (CBT). 73 patients with agoraphobia with or without panic disorder were included in the study. Heart rate (HR) and HRV were recorded at rest before and after CBT and during in-vivo exposure. No changes in HR and HRV were observed throughout therapy. During in-vivo exposure HRV increased significantly and HR exhibited a tendency to decrease. Despite clinical improvement of anxiety symptoms, ANS activity at rest did not seem to be influenced by CBT. However, during in-vivo exposure, HRV changed significantly, indicating a higher parasympathetic activity at the end of exposure.

1. Introduction

The fluctuation of heart-beat intervals is called heart rate variability (HRV) and is an important measure for the investigation of the sympathetic and parasympathetic pathways of the autonomic nervous system (ANS). Measuring HRV allows us to gain insight into the activity of the ANS without using invasive methods.

HRV comprises different parameters, which can largely be divided into either time domain measures or frequency domain measures (Task Force, 1996). The most commonly used time domain measure parameter is called the square root of the mean squared differences of successive NN intervals (RMSSD) (Task Force, 1996). The RMSSD is a convenient parameter due to its robustness against breathing factors (Hill & Siebenbrock, 2009). Frequency domain measures are achieved through spectral analysis methods, often using fast Fourier transformation (Quintana, Alvares, & Heathers, 2016). Several frequency bands have been defined, for example, the high frequency band (HF HRV) with a frequency range of 0.15-0.4 Hz, the low frequency band (LF HRV) with a frequency range of 0.04-0.15 Hz and the very low frequency band (VLF HRV) with a frequency range of 0.003-0.04 Hz. HF HRV and RMSSD are two different markers for parasympathetic nervous system activity. In some studies, it is assumed that LF HRV represents sympathetic activity (Malliani, Pagani, Lombardi, & Cerutti, 1991; Pagani et al., 1986), however, most studies consider LF HRV to be influenced by sympathetic and parasympathetic factors (Berntson et al., 1997; Birkhofer, Schmidt, & Forstl, 2005). The authors of a review dealing with this topic (Reyes del Paso, Langewitz, Mulder, van Roon, & Duschek, 2013) suggest that LF HRV might mainly be influenced by parasympathetic influences. Currently, no final agreement on the interpretation of LF HRV has been reached. VLF HRV seems to be related to hormonal processes and thermal regulation (Birkhofer et al., 2005; Laborde, Mosley, & Thayer, 2017).

It has been well researched that patients with anxiety disorders have a lower HRV at rest compared to healthy controls (Chalmers, Quintana, Abbott, & Kemp, 2014). One explanation for this is the neurovisceral integration model (Thayer & Lane, 2000). According to this model, a

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nervous system that can adapt appropriately to environmental and inner demands is associated with a higher HRV. Parasympathetic activity seems especially important for the ability to process information adequately and respond appropriately (physiologically as well as emotionally). This flexibility seems to be lacking in patients with anxiety disorders and appears to stand out in a lower HRV (Friedman & Thayer, 1998; Friedman, 2007).

Furthermore, a low HRV appears to be a risk factor for cardiac disease. In their meta-analysis, Buccelletti et al. (2009) showed that the risk of fatal outcomes after myocardial infarction is four times higher in patients with a low HRV (OR = 3.95). Several reviews indicate a relationship between low HRV and cardiovascular disease in patients with anxiety disorders (Celano, Daunis, Lokko, Campbell, & Huffman, 2016; Gorman & Sloan, 2000; Kemp & Quintana, 2013; Ouakinin, 2016).

Given this known risk, the question arises if HR and HRV of patients with anxiety disorders can be influenced. Cognitive behavioral therapy (CBT) changes the way patients deal with anxiety. They gain new flexibilities, by giving up avoidance behavior, testing out fears and withstanding anxiety and its symptoms (Kaczkurkin & Foa, 2015).

To date, there are only a few studies investigating the effects of CBT on HR and HRV, revealing inconsistent findings. Diveky et al. (2013) treated 31 inpatients with panic disorder (PD) with six weeks of CBT. HRV was recorded in two different positions (first in a supine position, then standing and lastly in a supine position again) before and after therapy. The authors found a significant increase in the VLF HRV band in the standing position after therapy and a reduction of the (VLF + LF)/HF ratio in the last supine position. They suggest that this may indicate an increase in parasympathetic activity. No significant changes could be found in the other positions or for HF HRV and LF HRV. Garakani et al. (2009) reported a significant increase in HRV and a decrease in HR after a 12-week CBT program for patients with PD, but only for those patients without ongoing pharmacotherapy. Middleton and Ashby (Middleton & Ashby, 1995) treated 22 patients with PD with CBT or imipramine. The findings of the study revealed a significant increase in HRV (measured ˜0.1 Hz) after at least three months of CBT or imipramine. In contrast, Mussgay and Rüddel (2004) tested 38 patients with agoraphobia and or PD after 42 days of rehabilitation therapy. Results revealed no significant changes in HR or HRV. Prasko et al. (2011) treated 19 inpatients with PD with 18 sessions of CBT and selective serotonin reuptake inhibitors (SSRI). HRV was recorded in 3 positions (supine, standing, supine) and their findings show a significant increase of the first supine measurement of HF HRV. All other positions and indices of HRV remained unchanged.

A core element of CBT for patients with agoraphobia is in-vivo exposure. Here, patients learn to confront their fears, adapt to anxiety inducing situations and as such, broaden their behavioral repertoire (Foa & Kozak, 1986). This process might be accompanied by changes in ANS activity. In the beginning of an in-vivo exposure, the patient's anxiety level is high and ANS activity, in theory, should predominantly be influenced by sympathetic activity. At the end of exposure, the patient's anxiety level reduces, and the parasympathetic activity theoretically takes over (Davies, Esler, & Nutt, 2010; Kaczkurkin & Foa, 2015). If this is the case, it should be reflected in an increase of HF HRV and RMSSD at the end of exposure. To our knowledge, no previous studies have examined the response of HR and HRV in patients with agoraphobia with or without PD to in-vivo exposure involving CBT. One case-study detected a significant relationship between subjective anxiety and HR during in-vivo exposure, but authors did not report the course of HR during in-vivo exposure (Lewis & Drewett, 2006).

Given the risks associated with a low HRV as displayed in patients with anxiety disorders and the present lack of research and inconsistencies of results, the aim of the present study was to investigate if HR and HRV change throughout CBT sessions and during in-vivo exposure. More specifically, it was hypothesized that HR at rest decreases from the beginning to the end of CBT, whereas HF HRV and RMSSD at rest increase from the beginning to the end of CBT. Regarding in-vivo exposure, HR should be lower at the end of exposure, compared to the beginning. Furthermore, RMSSD and HF HRV should be higher at the end of exposure, than at the beginning.

2. Material and methods

The present study is a secondary analysis of an already accepted randomized controlled trial investigating the augmenting effect of D-cycloserine (DCS) compared to a placebo on CBT with in-vivo exposures (Pyrkosch et al., 2018). It is a multi-center study, conducted at the Charité-Universitätsmedizin Berlin and the Humboldt Universität zu Berlin. Study registration (ClinicalTrials.gov Identifier: NCT01928823) and approval from the ethics committee was obtained on 27.06.2011 from the State Office of Health and Social Affairs Berlin (Eudra-CT: 2011-001398-19).

2.1. Participants

73 patients with a mean age of 37.53 years were included in the study. Patients were recruited at the specialized outpatient clinic for anxiety disorders at the Charité - Universitätsmedizin Berlin and met diagnostic criteria of agoraphobia with or without PD according to the ICD-10 (Dilling & Freyberger, 2017). All patients gave written informed consent. Before patients were included in the study medical history was checked and severely physically ill patients were not invited for further examination. Afterwards all patients underwent a physical examination at the Charité-Universitätsmedizin Berlin, including anamnesis, laboratory analysis and electrocardiogram in order to exclude patients with serious diseases.

Four patients were excluded from HR and HRV analyses due to use of beta blockers and three other patients were excluded due to cardiovascular diseases. Cardiac data observed before and after therapy at rest from 29 patients were analyzed and HR and HRV data during in-vivo exposure from 27 patients were investigated. Those two subsamples overlap partially. Eleven patients were included in both analyses. There was no significant difference between the two subsamples regarding descriptive statistics (age, diagnose, sex, DCS or placebo, education, or psychopharmacotherapy). For an overview of included patients and reasons for missing and excluded data see Fig. 1.

Psychiatric diseases were assessed using IDCL Checklists (Hiller, Zaudig, & Mombour, 1994) and the SKID II (Fydrich, Renneberg, Schmitz, & Wittchen, 1997). 31 patients had an ongoing psychopharmacological therapy. Psychopharmacological therapy had to be stable for at least four weeks before the beginning of the study and was not allowed to be changed during the trial. For sociodemographic data see Table 1.

2.2. Procedure

Patients underwent a manualized CBT including three exposure sessions. The manual was similar to validated CBT programs (Gloster et al., 2009; Lang, Helbig-Lang, Westphal, Gloster, & Wittchen, 2012; Margraf & Schneider, 1990). The 22 therapists were all psychologists with a master's degree and at least in the first year of their advanced training in psychotherapy. They were trained in using the manual and received constant supervision. Altogether, patients took part in twelve sessions (time points: T1-T12). The first four sessions were used for assessments (T1-T4) and at T4 a resting measurement of HR and HRV was conducted. Six CBT sessions (T5-T10) followed, which included three in-vivo exposures (T7-T9). For high fear inducing exposures, situations were chosen individually for each patient to ensure best in-vivo exposure opportunities. Only agoraphobic situations were chosen for exposures and no interoceptive exposures were conducted. Most often included exposures were public transportation (underground, bus and train), elevators, driving cars on the highway or cinema and theatre

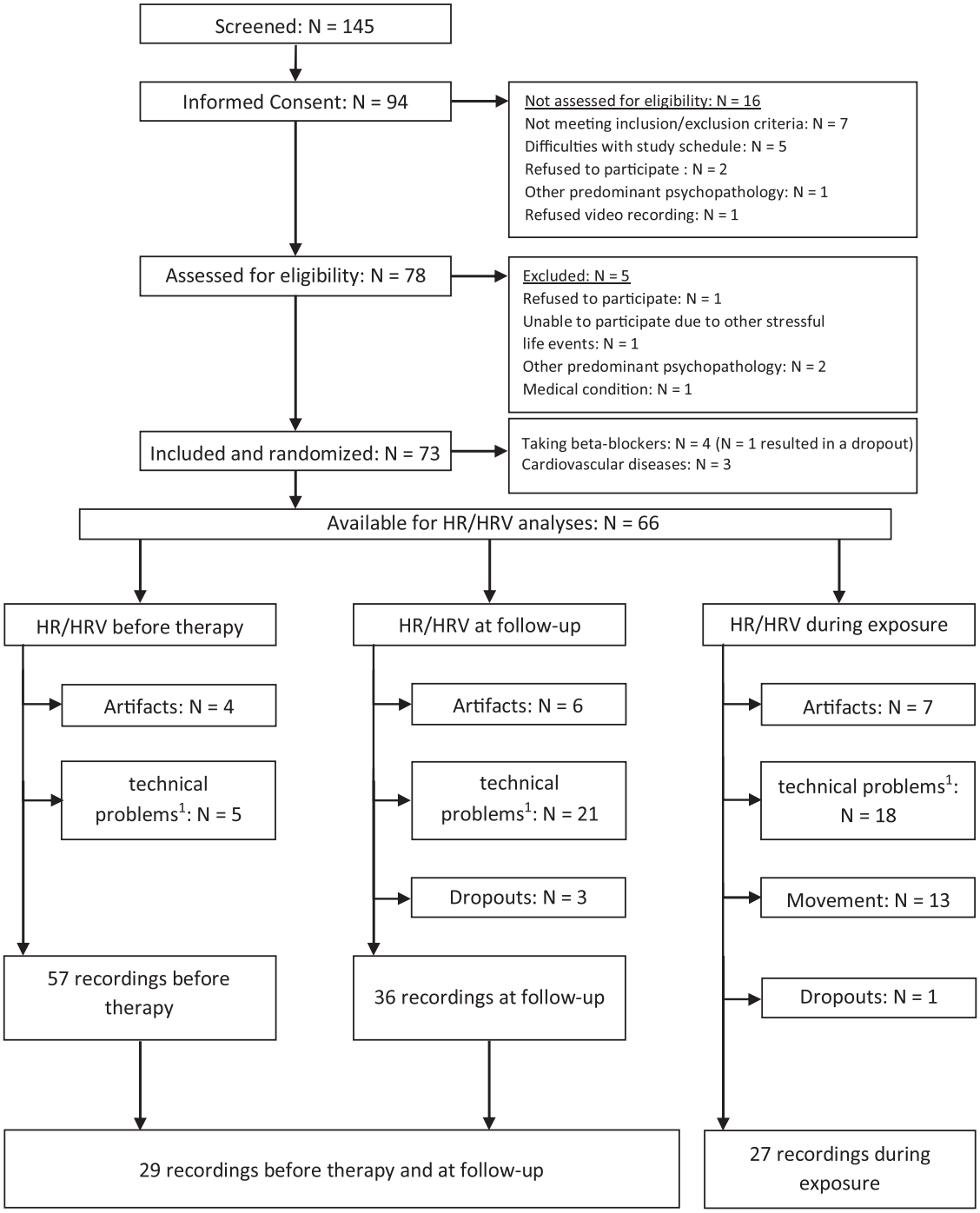

Fig. 1. Flow of patients.
[1]Technical problems include missing time protocols of beginning and end of exposure, problems of usage of HRV recording device and forgotten attachment of accelerometer.

visits. In each exposure session exposures were conducted twice, one right after the other and HR and HRV were recorded. After each of the three exposure sessions, a double-blind administration of either 50 mg D-cycloserine (DCS) or Placebo took place. This was followed by a one-month follow-up including two sessions (T11-T12). At T11 another resting measure of HR and HRV was implemented. For detailed information about the procedure see Pyrkosch et al. (2018).

2.3. HR and HRV measurements

To measure HR and HRV, patients wore the HRV recording device RS800CX and an accelerometer from Polar Electro Oy (Finland, Kempele). Therapists were trained in using technical equipment. RMSSD and HF HRV (frequency range from 0.15-0.4 Hz) were recorded as parameters of HRV. To ensure valid methodology, five-minute intervals were compared with each other, as recommended by the Task Force (1996) and to match the time period of several other published studies (Heathers, 2014).

For the recording of HR and HRV at rest before therapy (T4) and at follow-up (T11), patients were seated on a chair and instructed to sit calmly.

During exposure sessions (T7-T9) HR and HRV were also recorded.

Table 1
Demographic Data.

	All patients (N = 73)
Age	*M* = 37.53 (*SD* = 12.15)
Sex	
Female	48 (65.75%)
Male	25 (34.25%)
Treatment group	
DCS	36 (49.32%)
Placebo	37 (50.68%)
Education	
No high school diploma	24 (32.88%)
High school diploma or higher	49 (67.12%)
Psychopharmacotherapy	
No	42 (5753%)
Yes*	31 (42.47%)
SSRI	22 (30.14%)
Tricyclic Antidepressants	6 (8.22%)
Other	5 (6.85%)

Note: *some patients had more than one psychopharmacological medicine, M = mean, SD = standard deviation, SSRI = selective serotonin reuptake inhibitor, DCS = D-cycloserine.

Therapists wore a watch displaying the exact same time as the patients' HRV recording device. They kept a protocol of exposures and noted the exact time of the beginning and end of each exposure, therefore making it possible to determine HR and HRV of the first and the last five minutes of each exposure. In addition, therapists kept a protocol of the patients' anxiety scores during exposure. For this, a visual analogue scale (from 0 = no anxiety to 10 = maximum anxiety) was employed. For the analyses of HR and HRV during exposure, only movement-free five-minute intervals were used to prevent confounding factors of motion on cardiac data. The minute before a five-minute interval also had to be movement-free. All other data were excluded from the analysis. Regarding the beginning of exposure, the analyzed five minutes started within the feared situation after one movement-free minute. To qualify as the beginning of the exposure movement-free intervals had to start at least three minutes after entering the feared situation. Otherwise, the exposure was excluded from the analyses. In most of the included cases there was no movement after the first minute of the beginning of the exposure (movement after minute 1 occurred in only 4 cases and of those cases only one occurred in minute 2). Mean overall exposure duration was 73 min. The last five minutes within the exposure situation served as the end of exposure. Movement was measured with an accelerometer from Polar, which was connected to the used recording device RS800CX.

To retrieve HR and HRV, data was pre-processed with the programs Polar ProTrainer 5 (Polar ProTrainer, 2019) and Kubios HRV from the University of eastern Finland (Tarvainen, Niskanen, Lipponen, Rantaaho, & Karjalainen, 2014). Firstly, data was downloaded from the recording device with Polar ProTrainer 5. Filter power was set to moderate and the minimum protection zone was set to 6. Furthermore, data was visually inspected for artifacts with the help of a cardiologist. Afterwards HR, RMSSD and HF HRV were extracted for selected five-minute intervals using the software Kubios HRV. For the present paper, only data of the first exposure in the first exposure session was analyzed, as this was the only exposure without any DCS or Placebo influences (medication was administered after exposures).

2.4. Questionnaires

Questionnaires were filled out at four time points: during the initial diagnostic session (T1), right before the first therapy session (T4), during the last therapy session, (T10) and at follow-up (T11). To measure treatment success the "Panic and Agoraphobia Scale" (PAS), self-rating and clinician-rating versions (Bandelow, 1997) were used. The questionnaires comprise main symptoms of agoraphobia and PD and were developed to measure changes due to treatment. With the "Agoraphobic Cognitions Questionnaire" (ACQ), the "Body Sensations Questionnaire" (BSQ), and the "Mobility Inventory" (MI) (Chambless, Caputo, Bright, & Gallagher, 1984; Ehlers & Margraf, 2001) three specific problems of patients with agoraphobia are examined in detail (all self-rating). The ACQ illustrates the presence and intensity of specific cognitions when patients are anxious. The BSQ explores how much anxiety or worry is caused by typical agoraphobic bodily symptoms and the MI describes how many situations are avoided (alone or accompanied) due to agoraphobia. Using the self-rating questionnaire "Anxiety Sensitivity Index" (ASI) (Reiss, Peterson, Gursky, & McNally, 1986), a global (not specific to agoraphobia) tendency to evaluate specific anxiety related statements (for example not being able to focus on a task or blushing in front of others) as harmful or worrying can be assessed. The "Beck Anxiety Inventory" (BAI) (Beck & Steer, 1993; Beck, Epstein, Brown, & Steer, 1988) utilizes cognitive and physiological symptoms to measure the degree of anxiety severity. It is a self-rating questionnaire. The "Beck Depression Inventory II" (BDI) (Beck, Steer, Ball, & Ranieri, 1996) explores the presence and severity of depressive symptoms in a self-rating. To evaluate the psychological stress of each patient the "Brief Symptom Inventory" (BSI) (Franke, 2000) was used. Lastly, the "Clinical Global Impression" (CGI) (Guy, National Institute of Mental, H., Psychopharmacology Research, B., Early Clinical Drug Evaluation, & P., 1976) was rated by therapists to have an impression of the severity of agoraphobia. Only patients with a CGI higher than 4 were included in the trial. The PAS was set as the primary clinical outcome criterion of the present study.

2.5. Statistical analyses

SPSS statistics 24 was used to analyze the data.

Firstly, normal distribution was examined for all HR and HRV measurements with the Kolmogorov-Smirnov test. Non-normal data was log transformed (to base 10).

To determine if psychopharmacological therapy or sex had an influence on HR or HRV parameters, t-tests were conducted comparing patients with and without psychopharmacological treatment and men and women. If significant, psychopharmacotherapy and/ or sex were included as between subject factors to the corresponding repeated measures ANOVAs.

To detect correlations between age and HR, RMSSD or HF HRV, a Pearson's correlation was performed. If a significant relationship was found, age was added as a covariate to the corresponding repeated measures ANOVAs. Homogeneity of variances was examined with help of the Levene's-test.

To examine differences regarding HR, RMSSD and HF HRV in patients with agoraphobia with or without comorbid PD Mann-Whitney tests were calculated. To determine if patients had improved from therapy, a dependent *t*-test was conducted with PAS clinician-rating scores from the last diagnostic session (T4) and follow-up (T11). To detect differences between HR and HRV at rest before and after therapy, 2 × 2 repeated measures ANOVAs with time (HR and HRV at T4 = before therapy, HR and HRV at T11 = after therapy) as the within subject factor and group (DCS, Placebo) as the between subject factor were conducted.

For the first exposure, repeated measures ANOVAs with time (HR and HRV at the beginning of the first exposure, HR and HRV at the end of the first exposure) as a within subject factor was calculated. Patients with or without psychopharmacotherapy displayed significantly different RMSSD and HF HRV scores. Therefore, psychopharmacotherapy (psychopharmacotherapy/ no psychopharmacotherapy) was added as a between subject factor to the ANOVAs for RMSSD and HF HRV.

Bonferroni corrected exploratory analyses were conducted to examine correlations between questionnaires and HR and HRV measurements before therapy.

Significance level was set at alpha < 0.05 (two-tailed).

3. Results

3.1. HR and HRV at rest before and after therapy

Dependent t-tests on PAS clinician-rating scores from before therapy and at follow-up revealed that on average, patients improved significantly from before therapy ($M = 21.22$, $SD = 8.59$) to follow-up ($M = 5.52$, $SD = 5.35$), $t(28) = 8.73$, $p < .01$.

Due to non-normality, HR and HF HRV scores were log transformed. Independent t-tests revealed no significant differences between patients with or without ongoing psychopharmacotherapy concerning HR (before therapy: $t(27) = -0.06$, $p = .95$; follow-up: $t(27) = 1.05$, $p = .30$), RMSSD (before therapy: $t(27) = 1.14$, $p = .27$; follow-up: $t(27) = 0.87$, $p = .39$) and HF HRV (before therapy: $t(27) = 1.74$, $p = .09$; follow-up: $t(27) = 0.81$, $p = .43$) before therapy and at follow-up.

For RMSSD (before therapy: $r = -.32$, $p = .09$; follow-up: $r = -.44$, $p = .02$) and HF HRV (before therapy: $r = -.30$, $p = .12$; follow-up: $r = -.53$, $p < .01$) significant correlations with age were found. Thus, age was added as a covariate to the corresponding ANOVAs. No significant correlation was found between HR and age (before therapy: $r = .09$, $p = .63$; follow-up: $r = .10$, $p = .61$).

Regarding sex, independent t-tests found no differences for RMSSD (before therapy: $t(27) = 0.75$, $p = .46$; follow-up: $t(27) = -0.14$, $p = .89$), HF HRV (before therapy: $t(27) = 0.56$, $p = .58$; follow-up: $t(27) = 0.29$, $p = .78$) and HR (before therapy: $t(27) = -1.33$, $p = .20$; follow-up: $t(27) = 0.47$, $p = .64$) between men and women.

Mann-Whitney tests comparing HR, RMSSD and HF HRV of patients with agoraphobia without PD and patients with agoraphobia with PD revealed no significant differences (before therapy: HR: $U = 33.00$, $p = .054$, RMSSD: $U = 52.00$, $p = .38$, HF HRV: $U = 62.00$, $p = .73$, follow-up: HR: $U = 48.00$, $p = .28$, RMSSD: $U = 67.00$, $p = .94$, HF HRV: $U = 67.00$, $p = .94$). DCS or placebo was added as a between subject factor to all three ANOVAs, as patients were treated with DCS or placebo during the course of CBT.

Repeated measures ANOVAs revealed no significant within-subject or between-subject effects or interactions for HR and HRV parameters (see Table 2). Levene's tests were not significant, indicating that the assumption of homogeneity of variances was not violated.

3.2. HR and HRV during exposures

Due to violations of normal distribution RMSSD and HF HRV were log transformed. HR was normally distributed.

Significant differences in HF HRV and RMSSD scores were found at the beginning and at the end of exposure between patients without ongoing psychopharmacotherapy and patients with ongoing psychopharmacotherapy (HF HRV: beginning: $t(25) = 3.12$, $p < .01$; end: $t(25) = 3.30$, $p < .01$; RMSSD: beginning: $t(25) = 3.14$, $p < .01$; end: $t(25) = 3.62$, $p < .01$). Therefore, psychopharmacological treatment was included as a between subject factor for the ANOVAs for RMSSD and HF HRV. Independent t-tests revealed no significant differences between HR of patients with or without psychopharmacotherapy (beginning: $t(25) = -0.52$, $p = .61$; end: $t(25) = -0.74$, $p = .47$).

Age correlated significantly with HR (beginning: $r = -.44$, $p = .02$; end: $r = -.46$, $p = .02$). Therefore, age was included as a covariate in the ANOVA analyzing HR. There were no significant correlations between age and RMSSD scores (beginning: $r = -.27$, $p = .17$; end: $r = -.22$, $p = .28$) and HF HRV scores (beginning: $r = -.24$, $p = .22$; end: $r = -.33$, $p = .09$).

For sex independent t-tests revealed no significant differences between men and women regarding HR (beginning: $t(25) = -0.32$, $p = .75$; end: $t(25) = -0.78$, $p = .45$), RMSSD (beginning: $t(25) = 0.08$, $p = .94$; end: $t(25) = 0.23$, $p = .82$) and HF HRV (beginning: $t(25) = 0.28$, $p = .78$; end: $t(25) = 0.01$, $p = .99$).

HR, RMSSD and HF HRV did not differ in patients with or without comorbid PD (beginning: HR: $U = 62.00$, $p = .98$, RMSSD: $U = 47.00$, $p = .38$, HF HRV: $U = 44.00$, $p = .29$, end: HR: $U = 55.00$, $p = .67$, RMSSD: $U = 48.00$, $p = .41$, HF HRV: $U = 44.00$, $p = .29$).

Within-subject results of repeated measures ANOVAs revealed a significant increase of HF HRV and RMSSD from the beginning to the end of exposure. Furthermore, there was a trend towards significant decrease in HR from the beginning to the end of exposure (see Table 3).

During exposure, patients with psychopharmacotherapy showed significantly reduced HF HRV and RMSSD scores compared to patients without psychopharmacotherapy (RMSSD: $F(1, 25) = 12.43$, $p < .01$, $\eta_p^2 = .33$ and HF HRV: $F(1, 25) = 11.39$, $p < .01$, $\eta_p^2 = .31$). No significant interactions were found. Levene's tests were not significant, indicating that the requirements for homogeneity of variances were met.

3.3. Exploratory analysis

There were no significant correlations between disease duration and HR and HRV measurements before therapy: HR: $r = -.10$, $p = .45$, RMSSD: $r = -.20$, $p = .13$ and HF HRV: $r = -.17$, $p = .20$. Additionally, no significant correlations were found between questionnaires and HR or HRV measurements before therapy (see Table 4).

4. Discussion

Contrary to our hypotheses, HR and HRV at rest did not change from the beginning to the end of CBT. However, during in-vivo exposure HR exhibited a tendency to decrease and HF HRV and RMSSD increased significantly. The results of the present study do not support the hypothesis that CBT changes HR and HRV at rest. Thus, CBT might not reduce cardiovascular risks associated with a reduced HRV, as known for patients with PD. Since modulation of ANS activity is not yet fully understood, it remains unclear as to why the enhancing effect of CBT could only be found in some studies. Furthermore, the interaction of biological processes (like HRV) and changes happening during CBT or directly during in-vivo exposure (like reappraisal or learning processes) is not known yet and it is quite unclear if one process precedes another. Regarding that point, our results are in line with literature showing the inconsistency of HRV changes despite treatment effects. Patients in our trial showed a significant reduction of symptom severity measured with different questionnaires after therapy. Nevertheless,

Table 2
Repeated measures ANOVAs with HR and HRV at rest before therapy and at follow-up.

	Before therapy		Follow-up		*F*-statistics	*p*	*df*	Partial η_p^2
	M	*SD*	*M*	*SD*				
Log HR	1.87	0.06	1.88	0.07	$F = 0.91$	.35	1	.03
HR	74.96	10.13	76.73	11.97				
RMSSD	35.03	21.09	29.54	16.49	$F = 0.01$	.93	1	.00
Log HF HRV	2.47	0.59	2.34	0.55	$F = 0.24$	.63	1	.01
HF HRV	548.79	508.88	435.41	575.36				

Note: N = 29; M = mean, SD = standard deviation, Log refers to log transformed variables.

Table 3
Repeated measures ANOVAs with HR and HRV during exposure.

	Beginning of exposure		End of exposure		*F*-statistics	*p*	*df*	Partial η_p^2
	M	*SD*	*M*	*SD*				
HR	99. 12	16. 77	90. 88	13. 22	$F = 3.34$	.08	1	.12
Log RMSSD	1. 21	0. 25	1. 27	0. 22	$F = 6.04$	.02	1	.20
RMSSD	19. 01	9. 93	21. 22	11. 01				
Log HF HRV	2. 01	0. 57	2. 17	0. 47	$F = 8.47$	.007	1	.25
HF HRV	201. 74	215. 89	254. 21	281. 89				

Note: N = 27, * = p < .05; M = mean, Log refers to log transformed variables.

Table 4
Exploratory analyses before therapy.

	HR	*p*	RMSSD	*p*	HF HRV	*p*
PAS clinician-rating	.11	.44	−.01	.96	.01	.94
PAS self-rating	.08	.57	−.02	.88	−.04	.78
CGI	.04	.77	−.09	.49	−.04	.78
ACQ	−.10	.48	.19	.16	.18	.19
BSQ	−.14	.30	.12	.39	.16	.22
MI_a	.07	.60	.04	.79	.01	.92
MI_b	.17	.21	.05	.73	.05	.71
ASI	.12	.93	.10	.48	.12	.37
BAI	.19	.17	−.11	.43	−.09	.49
BDI	.09	.53	.03	.80	.01	.95
BSI	.18	.18	−.01	.96	.00	> .99

Note: Pearson's correlations; N = 57; Bonferroni-corrected alpha < .005.

HRV did not change. Therefore, currently there is not enough evidence to see HRV as an indicator of symptom improvement in patients with agoraphobia with or without PD.

Several potential explanations for the current results must be considered. Firstly, patients in the present study could have had too many symptoms at follow-up. Nine out of 32 patients still had mild symptoms, one displayed medium symptoms and 22 showed remission or were partially remitted according to the PAS clinician-rating. Therefore, a longer and more stable remission period may be necessary to achieve ANS changes, as shown by Garakani et al. (2009) and Middleton and Ashby (1995) (both treated patients with 12-weeks of CBT). In contrast, Mussgay and Rüddel (2004) and Diveky et al. (2013) performed CBT of only 6-weeks and 42 days, respectively. The first trial did not find any significant changes in HRV, however Diveky et al. (2013) found some significant changes in the VLF band, but not in HF HRV or LF HRV.

Secondly, genetic components could be involved in a person's HRV, as stated by a recent review (Nolte et al., 2017). It might be that some aspects of HRV are genetically determined and are thus not able to be positively influenced by CBT. A study supporting this showed that pregnant women, who had a former PD, still had a lower HRV than pregnant women without a previously diagnosed PD. Furthermore, the children of mothers with a former PD displayed lower HRV compared to those with mothers who had never suffered from PD (Braeken et al., 2013).

During in-vivo exposure, HR and HRV changed from the beginning to the end. RMSSD and HF HRV increased, whereas HR showed a trend towards decrease. This indicates an increase of parasympathetic activity at the end of exposure, resulting in a greater flexibility of reactions, enabling patients to respond adequately to stimuli and experience less anxiety. These results parallel theoretic assumptions of extinction learning. That is, patients learn to adapt to a feared situation and, if successful, are able to remain in the feared situation without anxiety. This means that they are able to cope with their previously automatic fear response. Despite the significant change of autonomic activity during in-vivo exposure, that could be seen as a successful autonomic response, it does not seem to be sufficient to change reduced autonomic flexibility at rest. Patients might need to practice feared situations successfully more often for it to have lasting effects on ANS activity.

Interestingly, resting HRV was not affected by psychopharmacotherapy. This result is supported by findings of a meta-analysis comparing the impact of psychotropic medication on HRV in different mental diseases showing that resting HRV only decreased in patients with mood disorders, but not in patients with anxiety disorders (Alvares, Quintana, Hickie, & Guastella, 2016). The authors reported that only tricyclic antidepressants had a reducing effect on HRV but not SSRIs. This might explain why in the present sample, with only 8% of the patients taking tricyclic antidepressants, resting HRV did not further decrease with psychopharmacotherapy.

It is an interesting pattern that despite equal resting HRV values patients with and without psychopharmacological treatment differ during exposure regarding RMSSD and HF HRV, with patients in the group with psychopharmacotherapy having lower values. To our knowledge there are currently no published studies available examining HRV in patients with and without psychopharmacotherapy in the context of exposures.

There might be two possible explanations that cannot be verified with our sample and need further investigation. One hypothesis is based on the fact that patients with psychopharmacotherapy exhibited lower anxiety levels at the beginning of exposure ($M = 3.75$) compared to patients without psychopharmacotherapy ($M = 5.09$). Having higher anxiety levels when being confronted with an agoraphobic threat (as is the case at the beginning of exposure) might be an adaptive response when someone is suffering from agoraphobia and goes along with a higher HRV. Psychopharmacological treatment might reduce the psychophysiological response and flexibility and could therefore be associated with lower anxiety levels and lower HRV during exposures. Another possible explanation might be the disease duration. Patients in the exposure sample receiving psychopharmacotherapy show longer disease durations compared to those patients without psychopharmacological treatment (M(with psychopharmacotherapy) = 102.29 and M (without psychopharmacotherapy) = 56.64). That might lead to a less flexible pattern of HRV and explain lower values during exposures.

4.1. Strengths and limitations

One limiting factor in the analyses of the cardiac data at rest could be that no healthy subjects were included in the study to ensure that patients' HRV was reduced at the beginning of therapy. Hence, the sample could have displayed an exceptionally high HRV before starting therapy. In comparison to suggested HRV norms of healthy adults by Nunan, Sandercock, and Brodie, (2010), RMSSD and HF HRV of the present study are lower: The medium RMSSD for healthy adults is suggested to be 42 ms and HF HRV 657 ms^2. Our sample showed a medium RMSSD of 34.87 ms and HF HRV of 548.74ms^2 before therapy. Due to the fact that many studies already confirmed the finding of a reduced HRV in patients with anxiety disorders (Chalmers et al., 2014) it was decided not to include healthy controls and to only examine if HR and HRV change over the course of CBT.

A further limitation is the number of missing data. This occured due to problems using the HRV recording device. In the future it would be

helpful to advise therapists while using technical equipment like HRV recording devices. Moreover, during exposure sessions, data acquired when patients were active had to be excluded from the analysis (for example: standing in lines and walking through shopping centers). This reduced the total amount of assessments included in the present study. Due to those facts, two different subsamples were analyzed. One for the analyses before and after therapy and the other for the analyses of the beginning and the end of exposure. Although, there were no significant differences regarding descriptive statistics between the two samples, there might be some undetected confounding variables.

One strength of the presented study is, that the situations used for in-vivo exposures were not standardized. For patients with agoraphobia, different situations cause anxiety. Therefore, patients had the opportunity to choose their highest anxiety inducing situation. This resulted in a high external validity. To our knowledge, this is the first study examining HR and HRV of patients with agoraphobia with or without PD in freely selected in-vivo exposures.

5. Conclusions

For a better insight on ANS activity in patients with agoraphobia with or without PD further research is needed. Regarding associated cardiovascular risks, mechanisms leading to a change of HRV from the beginning to the end of therapy seem to be very important. It may be beneficial to include more measurements at rest during the course of CBT and to track longer follow-up periods. Three in-vivo exposures may not be sufficient to change ANS activity at rest. Also, patients might need to practice exposures more often to have a lasting effect on resting ANS activity.

Declaration of interest

None.

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